**Nos. 22-2153, 23-1952**

In the United States Court of Appeals
For the Federal Circuit

SALIX PHARMACEUTICALS, LTD.,
SALIX PHARMACEUTICALS, INC.,
BAUSCH HEALTH IRELAND LTD., ALFASIGMA S.P.A.,
*Plaintiffs - Appellants*

v.

NORWICH PHARMACEUTICALS INC.,
*Defendant - Cross-Appellant*

On Appeal from the United States District Court for the
District of Delaware (Hon. Richard G. Andrews, presiding)
Case No. 1:20-cv-00430

# OPENING BRIEF OF APPELLANTS

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## CLAIMS AT ISSUE

Claim 3 of the ’667 Patent depends from Claim 1:

> 1. A method of treating one or more symptoms of irritable bowel syndrome (IBS) in a subject 65 years of age or older, said method comprising administering, 550 mg of rifaximin TID for 14 days to the subject, thereby treating one or more symptoms of IBS in the subject 65 years of age or older.
>
> 3. The method of claim 1, wherein the IBS is diarrhea-predominant IBS.

Claim 2 of the ’569 Patent depends from Claim 1:

> 1. A method of providing acute treatment for diarrhea-associated Irritable Bowel Syndrome (dIBS) comprising: administering 1650 mg/day of rifaximin for 14 days to a subject in need thereof, wherein removing the subject from treatment after the 14 days results in a durability of response, wherein the durability of response comprises about 12 weeks of adequate relief of symptoms.
>
> 2. The method of claim 1, wherein the 1650 mg is administered as 550 mg three times per day.

Claim 4 of the ’199 Patent provides:

> 4. Rifaximin in polymorphic form β, wherein the rifaximin has x-ray powder diffraction pattern peaks at about 5.4°; 9.0°; and 20.9° 2θ and wherein the rifaximin has a water content of greater than 5%.

Claim 36 of the ’206 Patent depends from Claim 34:

> 34. A solid pharmaceutical composition comprising rifaximin in polymorphic Form β and a pharmaceutically acceptable excipient or carrier, wherein the rifaximin Form β has x-ray powder diffraction pattern peaks at about 5.4°; 9.0°; and 20.9° 2θ.
>
> 36. The pharmaceutical composition of claim 34, wherein the rifaximin Form β has a water content of between about 4.5% to about 40%.

## CERTIFICATE OF INTEREST

| | |
|---|---|
| **Case Numbers** | 22-2153, 23-1952 |
| **Short Case Caption** | *Salix Pharmaceuticals, Ltd. v. Norwich Pharmaceuticals Inc.* |
| **Filing Party/Entity** | Salix Pharmaceuticals, Ltd., Salix Pharmaceuticals, Inc., Alfasigma S.p.A., Bausch Health Ireland Ltd. |

I certify the following information and any attached sheets are accurate and complete to the best of my knowledge.

*/s/ William R. Peterson*
William R. Peterson
*Counsel for Appellants*
*Salix Pharmaceuticals, Ltd.,*
*Salix Pharmaceuticals, Inc.,*
*Bausch Health Ireland Ltd., and*
*Alfasigma S.p.A.*

Dated: July 24, 2023

| **1. Represented Entities.** Fed. Cir. R. 47.4(a)(1). | **2. Real Party in Interest.** Fed. Cir. R. 47.4(a)(2). | **3. Parent Corporations and Stockholders.** Fed. Cir. R. 47.4(a)(3). |
|---|---|---|
| Provide the full names of all entities represented by undersigned counsel in this case. | Provide the full names of all real parties in interest for the entities. Do not list the real parties if they are the same as the entities.<br><br>☑ None/Not Applicable | Provide the full names of all parent corporations for the entities and all publicly held companies that own 10% or more stock in the entities.<br><br>☐ None/Not Applicable |
| Salix Pharmaceuticals, Ltd. | Not Applicable | Bausch Health Companies Inc. |

| | | |
|---|---|---|
| Salix Pharmaceuticals, Inc. | Not Applicable | Bausch Health Companies Inc. |
| Bausch Health Ireland Ltd. | Not Applicable | Bausch Health Companies Inc. |
| Alfasigma S.p.A. | Not Applicable | Turytes S.p.A. |

**4. Legal Representatives.** List all law firms, partners, and associates that (a) appeared for the entities in the originating court or agency or (b) are expected to appear in this court for the entities. Do not include those who have already entered an appearance in this court. Fed. Cir. R. 47.4(a)(4).

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**5. Related Cases.** Other than the originating case(s) for this case, are there related or prior cases that meet the criteria under Fed. Cir. R. 47.5(a)?

☑ Yes ☐ No ☐ N/A (amicus/movant)
(*See* Notice of Related Case Information at Dkt. 9 in No. 23-1952.)

**6. Organizational Victims and Bankruptcy Cases.** Provide any information required under Fed. R. App. P. 26.1(b) (organizational victims in criminal cases) and 26.1(c) (bankruptcy case debtors and trustees). Fed. Cir. R. 47.4(a)(6).

☑ None/Not Applicable

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## STATEMENT OF RELATED CASES

*Norwich Pharmaceuticals, Inc. v. Becerra et al.*, No. 1:23-cv-01611 (D.D.C.), is a pending suit by Norwich against the FDA because of the FDA's compliance with the judgment that is the subject of this appeal.

## STATEMENT OF JURISDICTION

The district court had federal question jurisdiction under 28 U.S.C. § 1331. The district court entered a final judgment on August 10, 2022. Appx50. Appellants filed a timely notice of appeal on August 16. Appx3965.

On September 7, Appellee Norwich Pharmaceuticals Inc. moved to modify the judgment under Federal Rule of Civil Procedure 60(b), Appx3968; Appx3970, which suspended the appeal. Fed. R. App. P. 4(a)(4)(A)(iv).

On May 17, 2023, the district court denied Norwich's motion to modify the judgment. Appx52. Norwich filed a timely appeal of the final judgment and denial of the motion to modify on May 19. Appx4243. This Court consolidated these appeals. No. 22-2153, Dkt. 20.

This Court has jurisdiction over this appeal of a final decision of a district court in this civil action arising under the Patent and Trademark Act. 28 U.S.C. § 1295(a)(1).

## STATEMENT OF THE ISSUES

***Issues Concerning IBS-D Patents:***

Two patents claim methods of treating IBS-D using a specific dosage of rifaximin: 550 mg administered three times a day (1,650 mg per day) for 14 days.

1. In finding these claims invalid as obvious, the district court relied on a press release ("the RFIB2001 Press Release"), which quotes a named inventor and reports some results of a study that is discussed at length in the IBS-D Patents. Did the district court err by relying on the RFIB2001 Press Release as prior art under pre-AIA Section 102(a) without evidence that it reported work "by others"?

2. Even considering the RFIB2001 Press Release, the highest dosage for which the district court found prior art reported successful results in treating IBS-D was 1,200 mg per day. Did the district court err in applying this Court's "prior-art-range" cases to find a reasonable expectation of success in treating IBS-D using the claimed dosage (1,650 mg per day) because it was "within the known range"?

***Issue Concerning Polymorph Patents:***

Two patents claim rifaximin in a form labeled "polymorphic form β."

3. At the time of the patent filing, it was unknown whether rifaximin was even polymorphic, much less whether form β existed. Did the district court err in finding that a skilled artisan would have had a motivation and reasonable expectation of success in preparing the claimed rifaximin form β?

## INTRODUCTION

This appeal concerns three straightforward errors in invalidating claims as obvious. First, the district court relied heavily on a press release issued within one year of the IBS-D Patents' filing that quoted a named inventor and that disclosed high-level results of a study also discussed at length in the specifications. Norwich presented no evidence that this press release was "by others," as required by 35 U.S.C. § 102(a) [pre-AIA]. The district court erred by treating it as prior art.

Second, none of the prior art credited by the district court, including the press release, justified finding that a skilled artisan would have had a reasonable expectation of success in treating IBS-D with the specific dosage claimed in the IBS-D Patents: 1,650 mg/day. To the extent that the district court made such a finding—none was made expressly—it erred. The highest dosage for which the district court found prior art reported success in treating IBS-D was 1,200 mg/day. The dosage claimed by Salix was outside the range disclosed to be safe and effective.

Third, the district court clearly erred in finding a motivation and reasonable expectation of success in preparing rifaximin form β. No reference disclosed form β or taught that rifaximin was polymorphic. The opinion below expressly rejects the contrary analysis of *Pharmacyclics LLC v. Alvogen Pine Brook LLC*, 556 F.Supp.3d 377 (D. Del. 2021). Appx15 n.1. Having affirmed in *Pharmacyclics*, No. 21-2270, 2022 WL 16943006 (Fed. Cir. Nov. 15, 2022), this Court should reverse here.

## STATEMENT OF THE CASE

Appellants Salix Pharmaceuticals, Ltd., Salix Pharmaceuticals, Inc., and Bausch Health Ireland Ltd. are related companies that are parts of "one of the largest specialty pharmaceutical companies in the world committed to the prevention and treatment of gastrointestinal diseases." Appx4059. For two patents at issue, these appellants are the exclusive licensees of Appellant Alfasigma S.p.A. Appx187 ¶ 43. For convenience, we refer to all appellants collectively as "Salix."

For more than thirty years, Salix "has licensed, developed and marketed innovative products to improve patients' lives and arm health care providers with life-changing solutions for many chronic and debilitating conditions." Appx4059. Salix's flagship product—the antibiotic Xifaxan® (the brand name for the drug rifaximin)—provides important relief for a variety of conditions.

The Food and Drug Administration first approved Xifaxan in 200 mg tablets to treat travelers' diarrhea in 2004. Appx2. As a result of Salix's continued research and innovation, the FDA approved 550 mg tablets for treatment of hepatic encephalopathy ("HE") in 2010 and, following years of research and studies, for treatment of irritable bowel syndrome with diarrhea ("IBS-D") in 2015. *Id.*

This appeal involves challenges by Appellee Norwich Pharmaceuticals Inc. to the patents protecting Xifaxan. In December 2019, Norwich filed an Abbreviated

New Drug Application ("ANDA") seeking to make and sell generic rifaximin 550 mg tablets with the same indications and uses as Xifaxan. Appx1365; Appx1368.

Salix sued Norwich under the Hatch-Waxman Act in March 2020, alleging that Norwich's ANDA infringed more than two dozen patents listed in the Orange Book for Xifaxan. Appx1366. As often occurs, the parties agreed to simplify the case and limit the claims and defenses in dispute. Norwich voluntarily dismissed several claims for invalidity, and Salix stipulated that Norwich's then-pending ANDA label did not infringe numerous asserted claims. Appx3709.

By the time of trial, the case had been streamlined to three groups of patents: patents claiming a method of treating hepatic encephalopathy, U.S. Patent Nos. 8,642,573, 9,421,195, and 10,335,397 ("the HE Patents"); patents claiming a method of treating IBS-D, U.S. Patent Nos. 8,309,569 and 10,765,667 ("the IBS-D Patents"); and patents claiming rifaximin in polymorphic form β, U.S. Patent Nos. 7,612,199 and 7,902,206 ("the Polymorph Patents").

Following a five-day bench trial, the district court found that the asserted claims of the HE Patents were valid and infringed by Norwich. Appx46. This appeal involves the asserted claims of the IBS-D Patents and Polymorph Patents: although the district court held that Norwich's ANDA would induce infringement, it held the asserted claims of the IBS-D Patents and Polymorph Patents invalid as obvious.

## I. The IBS-D Patents

This appeal primarily concerns Salix's patents claiming methods for treating IBS-D. Salix raises two discrete arguments regarding these patents before this Court: (1) the erroneous treatment of a reference as prior art; and (2) the erroneous finding of an expectation of success in treating IBS-D using the claimed dosage. An understanding of these issues requires background about the art and the litigation.

### A. Background on IBS-D

Irritable bowel syndrome (IBS) affects millions of Americans. Appx3027-3028. It is "a functional bowel disorder in which abdominal pain or discomfort is associated with defecation or a change in bowel habit." Appx3024. Symptoms include "abdominal pain, bloating, frequency, urgency, gas, and changed bowel habits." Appx32. Roughly one-third of IBS patients suffer from IBS-D, in which diarrhea is predominant. Appx3143.

IBS is a "syndrome" rather than a "disease" because it describes a "collection of symptoms" without a "defined, single cause." Appx3140-41. Doctors diagnose IBS "based on a patient's subjective symptoms and the absence of finding other disorders." Appx3028. In other words, after ruling out other causes for the symptoms, doctors diagnose patients with IBS. No medical test—not blood analysis, colonoscopy, CT scan, or anything else—allows a doctor to verify whether a patient has IBS. Appx3029.

Even today, IBS is "a black box," and doctors do not know its underlying cause. Appx3026. Some hypotheses include a central nervous system defect, signaling defects in the enteric (gut) nervous system, inflammatory changes in the mucosa of the colon, bacterial alterations, genetic factors, and dietary triggers. Appx3026-3027; Appx32.

**1. In 2008, the medical community lacks treatments for IBS-D.**

With such uncertainty about its underlying cause, treating IBS-D is challenging. This was particularly true in February 2008, the priority date for the IBS-D Patents. *See* Appx33.

Before the FDA approved Xifaxan in 2015, doctors had no good options for the treatment of IBS-D. Appx3316 (noting the "big unmet need"). At the time of the patents in 2008, numerous therapies were being tried out of hope and desperation, without any real expectation that they would succeed.

The placebo effect makes identifying successful treatments difficult. Because doctors must rely on patients' "subjective assessment of symptoms," Appx3297, "a huge placebo effect" is "associated with using any therapy," Appx3295. One paper cautions that the placebo response rate for "a global improvement in IBS symptoms" was 36%. Appx6403 (discussing "a recently published meta-analysis"). Others suggest even higher: "The placebo response of up to 40–50% in IBS trials confounds interpretation of many drug studies." Appx5504.

Particularly because of the placebo effect, a "double-masked, randomized, placebo-controlled trial is the gold standard method to test the efficacy of a new treatment" for IBS-D. Appx6403.

In 2008, the only FDA-approved product for the treatment of IBS-D was alosetron, indicated only for women with severe IBS-D. Appx3033. Some doctors attempted to treat the diarrhea with Imodium and pain with Bentyl. Appx3032. Others experimented with antidepressants, speculating that they might help with brain-gut communications. Appx3033. Still others tried probiotics (which might affect the bacteria in the colon) or changes to a patient's diet. *Id.*

Some doctors resorted to antibiotics, including off-label use of 200 mg Xifaxan (rifaximin) tablets. Dr. Schoenfeld, Salix's expert at trial, explained that he tried it on patients "who had severe irritable bowel syndrome with diarrhea symptoms, who had failed multiple therapies, who were despairing because of how their symptoms impacted them." Appx3319. He did not expect success but tried it as "an experiment": "[B]ecause . . . you've already failed so many treatments and you're so miserable, I think there's some hope that we might try something, and let's see if it's beneficial, but this is like an experiment." *Id.*

**2. Some physicians publish "retrospective chart reviews" discussing treatment of IBS with rifaximin.**

Some physicians who tried treating IBS patients with rifaximin published papers based on "retrospective chart reviews." Appx3295. These publications are

"the very lowest level of [medical] evidence." *Id.* A retrospective chart review is not a scientific study that tests a hypothesis. Doctors instead review their notes on old patient charts and (retrospectively) attempt to classify whether, when, and how much patients improved. Appx3308.

By definition, a retrospective chart review is not randomized (the patients are not assigned treatments at random), not blinded (the doctor and patient both know what treatment the patient received), and not placebo-controlled (patients receiving treatment are not compared against patients receiving a placebo). Particularly given the "huge placebo effect" for IBS-D, one witness explained, a skilled artisan would not rely on a retrospective chart review "to provide accurate and unbiased results about the potential efficacy and safety of a treatment." Appx3295.

One such paper was published in March 2006 by Dr. Salvagini Cuoco. Appx4533 ("Cuoco"). It involved fewer than two dozen patients, who all received both 1,200 mg/day rifaximin and a probiotic. Appx3222. Cuoco is a retrospective chart review:

> The investigators went back and looked at their notes about bowel habits and what the patient said about their symptoms. And then in order to do a numeric comparison for symptom relief, they then assigned whether it was [0, 1, 2, or 3].

Appx3308. Like other retrospective chart reviews, Cuoco was not randomized, not blinded, and not placebo-controlled. Appx3221-3222 (discussing Appx4533).

Another retrospective chart review was published by Dr. George Barrett in September 2006. Appx4799 ("Barrett"). Barrett involved only eight patients. Like Dr. Cuoco, Dr. Barrett administered 1,200 mg/day rifaximin along with a probiotic. Appx3293; Appx4800. Barrett concludes that "further studies . . . are warranted." Appx4800.

### 3. Dr. Pimentel attempts treating IBS with antibiotics, but his work cannot be replicated.

Dr. Mark Pimentel, a clinician at the Cedars-Sinai Medical Center, was also researching treatments for IBS. Appx3115. He—along with others at Cedars-Sinai, Appx3276—theorized that "buildup of bacteria was a contributing factor to symptoms of irritable bowel syndrome" and thus attempted to treat IBS with antibiotics, Appx3117-3118.

In 2006, Dr. Pimentel published a study, which was conducted almost entirely at Cedars-Sinai, on the effects of treating IBS (not IBS-D) with 1,200 mg/day rifaximin. Appx4639 ("Pimentel 2006"). This was a randomized, double-blind, placebo-controlled study with 80 participants. *Id.*. According to Dr. Pimentel's calculations, "rifaximin recipients reported global improvements in overall symptoms and less bloating more frequently than placebo recipients." Appx4640. But "[n]o major differences in abdominal pain, diarrhea, or constipation were observed[.]" *Id.*

The broader medical community never accepted Dr. Pimentel's work. He was, in his own words, "the lone voice in the wilderness." Appx3117. Pimentel 2006, for example, involved idiosyncratic calculations, never used by any other study: "a very complicated biostatistical formula" that even a "master's degree recipient in health research methodology" could not understand. Appx3284.[1] In an editorial published alongside Pimentel 2006, Dr. Douglas Drossman—"one of the world's experts in irritable bowel syndrome," Appx3287—noted "several methodological issues" in Pimentel 2006 that made its "findings inconclusive and raise[d] questions about the clinical significance of the results," Appx5152-5153 ("Drossman").[2]

Dr. Pimentel's results—and those of his colleagues at Cedars-Sinai—could not be reproduced by other researchers. *E.g.*, Appx5152-5153 (noting differences in results); Appx5526 ("strongly cautions against antibiotic treatment for IBS patients"); Appx5546 (published study failing to duplicate results); Appx3281 ("I am not aware of a group in the U.S., certainly, that was able to replicate that [Cedars-Sinai] data.").

[1] No trial witness explained the calculations supporting the results reported in Pimentel 2006.

[2] *See also* Appx5543 ("[T]he most recent study by Pimentel and colleagues analysed the data using a complex statistical mixed model which creates a blending of symptom responses over the entire period rather than a conventional single end point.").

#### 4. In 2008, the medical community believes that insufficient evidence supports using rifaximin to treat IBS-D.

Several publications captured the mainstream medical view of the evidence at the time of the IBS-D Patents. A 2007 Education Practice note by Dr. Eamonn M.M. Quigley, Appx5537 ("Quigley"), stated, "sound rationale for antibiotic therapy has not been established," Appx3298. "[O]ne cannot yet recommend . . . empiric antibiotic therapy in IBS." Appx5537.

A 2007 publication from the British Society of Gastroenterology recognized that antibiotic treatment "cannot be recommended until replicated in well designed studies by others [i.e., doctors outside of Cedars-Sinai]." Appx5506.

A February 2008 article by Dr. Steve Vanner, Appx5539 ("Vanner"), surveyed the evidence, including "virtually every publication from the Cedars-Sinai group," Appx3300. He concluded that Dr. Pimentel's research (and other studies on using antibiotics to treat IBS-D) presented an "intriguing" but ultimately "unproven hypothesis." Appx5544. Less than a month before the priority date of the IBS-D Patents, Dr. Vanner wrote: "There is insufficient evidence to recommend antibiotics for the treatment of irritable bowel syndrome at present." Appx5543.

### B. Salix Investigates, Discovers, and Patents a Method of Treating IBS-D with 1,650 mg/day of Rifaximin

Against this backdrop of medical uncertainty, Salix conducted the first serious clinical research into the use of rifaximin for treating IBS-D. After a decade of

research and numerous clinical trials, Salix eventually received FDA approval for treating IBS-D with rifaximin.

**1. Salix conducts a Phase II clinical trial, "RFIB2001."**

Salix began by filing an investigational new drug application in November 2005. Appx3041. Shortly afterwards, Salix conducted a study called "RFIB2001," a "Phase II" clinical trial that tested a variety of different dosages and durations.[3] It was a randomized, double blind, and placebo-controlled study with more than 680 participants.

The protocol for the RFIB2001 study was published on ClinicalTrials.gov. DX340 (RFIB2001 Protocol). The study tested twice-daily doses of placebo, twice-daily doses of rifaximin 275 mg (550 mg/day), twice-daily doses of rifaximin 550 mg (1,100 mg/day) for both 14 and 28 days, and twice-daily doses of rifaximin 1,100 mg (2,200 mg/day). Appx7051; Appx7053.

The evidence at trial was that skilled artisans would not have an expectation of success merely because a Phase II clinical trial is being conducted. Appx3313-3314. Many Phase II trials do not yield positive results, Appx3314, and the RFIB2001 study was no exception. Its results were "confusing." Appx3042. The

[3] "RFIB2001" is the study's "Unique Protocol ID." Appx7050; *see also* Appx3173-3174. The district court included a space between "RFIB" and "2001." Although not explained in the record, it appears that "RF" indicates the drug and "IB" the target. The rifaximin–HE studies were labeled "RFHE." Appx2576.

study showed adequate relief of IBS symptoms using the 550-milligram-twice-daily dosage for 14 days but not from the same dosage for 28 days and not from the higher dosage (2,200 mg/day). Appx3042.

**2. Salix reports some results of RFIB2001 in a press release.**

On September 5, 2007, Salix reported some results of its RFIB2001 study in a press release (the "RFIB2001 Press Release"). Appx7480-7482. The press release reports success only for the 1,100-milligram-per-day dose:

> Top-line results of this study demonstrate that the . . . comparison of a 14-day dose of rifaximin at 550 mg twice-a-day [1,100 mg/day], provides a statistically significant improvement in both adequate relief of dIBS symptoms and adequate relief of bloating, compared to placebo.

Appx7480. Skilled artisans understood (correctly) that reporting success only for the 1,100 mg/day dosage indicated that the other dosages were unsuccessful. Appx3314.

Salix retained different IBS experts—including Dr. Schoenfeld, its expert witness at trial—to analyze the full results from the RFIB2001 study and conducted additional studies. Appx3042-3043.

**3. Salix conducts several Phase III clinical trials.**

In Phase III clinical trials initiated in June 2008, Salix tested 550 mg three times a day for 14 days. Appx3043. This is the same dosage claimed in the IBS-D Patents.

After its Phase III trials demonstrated improvement compared to the placebo, Salix submitted its new drug application to the FDA in June 2010. Appx3044. But the FDA rejected the sufficiency of Salix's data and required more studies. Appx5127 (March 2011).

On November 16, 2011, the FDA Gastrointestinal Drugs Advisory Committee met to discuss the design of additional clinical trials to evaluate the efficacy of rifaximin for IBS-D treatment. Appx5207. One member, Dr. Pasricha, questioned the "almost magical" 550 mg TID (three times daily) dosage identified by Salix. Appx5245; *see also id.* ("[A]nything over that doesn't work, anything less than that doesn't work[.]"); Appx5247 (noting that Salix had demonstrated a "U-shaped dose-response curve"). She noted the significant uncertainty about both IBS and rifaximin:

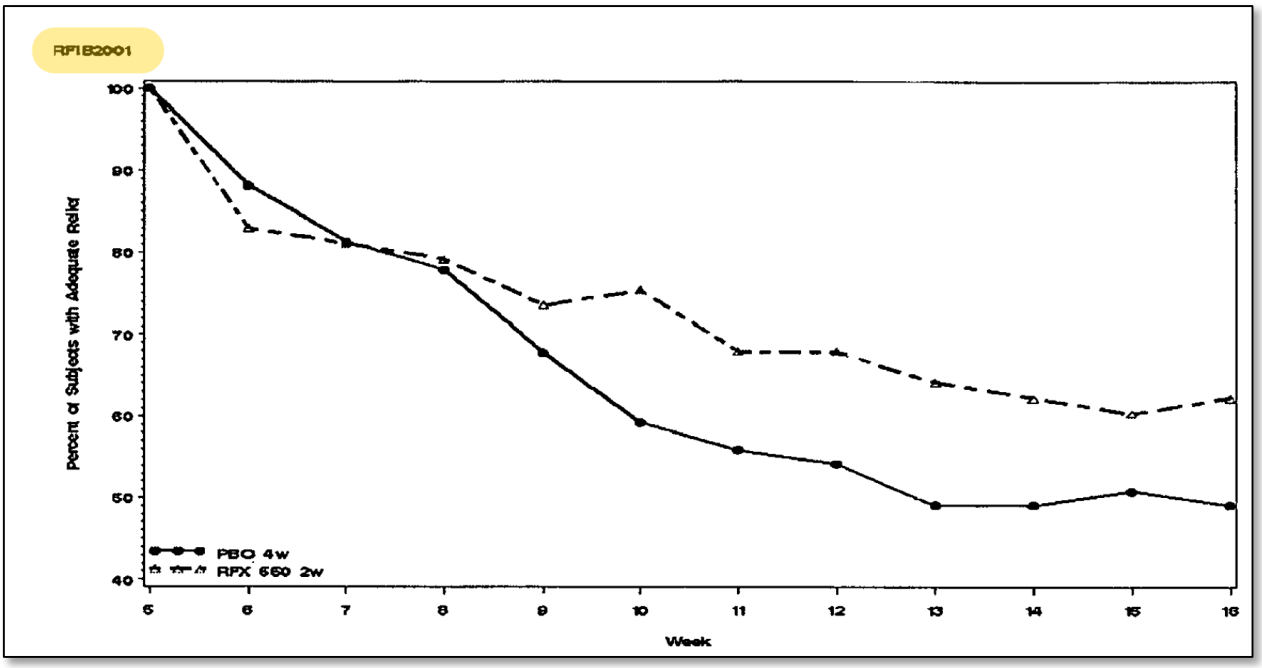
> [T]his is 2011. I know we don't know much about IBS, but we're basically . . . treating a disease which we know nothing or very little about with a drug that we know little or nothing about.

Appx5246.

Finally, in 2015, after Salix conducted an additional multiyear Phase III clinical trial, FDA approved rifaximin for the treatment of IBS-D at a dosage of 550 mg three times a day for 14 days.

**4. Salix patents the method of treating IBS-D with a specific rifaximin dosage (1,650 mg/day for 14 days).**

In February 2008, Salix filed patent applications that later became U.S. Patent Nos. 8,309,569 and 10,765,667. Both patents discuss the RFIB2001 study at length in their specifications. *See* Appx119, '569 Patent at 21:65-66 ("This example relates to a study of rifaximin in subjects with dIBS. Subjects received daily one of BID [twice-per-day] doses of placebo, rifaximin 275 mg, 550 mg, or 1100 mg for 14 days."); *see also* Appx119-121, '569 Patent at 21:65-25:52 (discussing RFIB2001 study and results); Appx151-153, '667 Patent at 23:63-27:56 (same). The figures in the '569 Patent are stamped "RFIB2001":



Appx103, '569 Patent, Fig. 1 (emphasis added); *see also* Appx104, Appx106-108.[4] Dr. Bill Forbes—the individual quoted discussing the results of "our study" in the RFIB2001 Press Release—is a named inventor on both patents.

Claim 3 of the '667 Patent and Claim 2 of the '569 Patent ("the IBS-D Claims") both involve a method of treating IBS-D with 550 milligrams of rifaximin three times per day (a total of 1,650 milligrams per day) for 14 days.[5]

### C. The District Court Holds the IBS-D Claims Invalid as Obvious

At trial, Norwich argued that the IBS-D Claims were obvious based on three combinations of prior art. For the '569 Patent, Norwich relied on the combination of Cuoco (Appx4533) and the RFIB2001 Protocol (Appx7047). For the '667 Patent, Norwich relied on the combination of Barrett (Appx4799) and the RFIB2001 Protocol. For both, Norwich relied on the combination of Pimentel 2006 (Appx4639) and the RFIB2001 Protocol. Because the district court found both IBS-D Claims obvious in view of the third combination, it did not address the others.

There is no dispute that skilled artisans knew of the general concept of trying off-label use of rifaximin to treat IBS-D. Salix, for example, was investigating rifaximin in the RFIB2001 study. And Salix's expert at trial, Dr. Schoenfeld,

[4] The figures in the '667 Patent are substantively identical but lack the "RFIB2001" stamp.

[5] Claim 2 of the '569 Patent includes the additional limitation of "about 12 weeks of adequate relief of symptoms" after stopping the treatment, and Claim 3 of the '667 Patent includes the additional limitation that the subject is "65 years of age or older."

testified that he treated some IBS-D patients with rifaximin (albeit at dosages below the claimed dosage) as an act of desperation. Appx3319; Appx3371.

The trial thus focused on narrower questions: (1) Would a skilled artisan have had a reasonable expectation of success in using rifaximin to treat IBS-D? and (2) More specifically, would a skilled artisan have had a reasonable expectation of success in using the claimed dosage (1,650 mg/day for 14 days) to treat IBS-D? After trial, the district court made two key findings:

> A POSA would have been motivated to combine the RFIB 2001 Protocol and Pimentel 2006 with a reasonable expectation of success.
>
> As of the priority date, the prior art disclosed positive results in using rifaximin to treat IBS-D for a range of doses. The asserted IBS-D claims describe a dosing regimen within the known range.

Appx33-34.

Two aspects of these findings warrant comment.

**1. The district court relies heavily on the RFIB2001 Press Release.**

Despite acknowledging the medical community's skepticism regarding using rifaximin to treat IBS-D, the district court found an expectation of success. In reaching this conclusion, the district court relied heavily on the RFIB2001 Press Release, which reported some results of Salix's RFIB2001 study.

The RFIB2001 Press Release was the heart of the district court's analysis: "Its disclosure of positive results would give a POSA a reasonable expectation of success in using rifaximin to treat IBS-D." Appx42; *see also, e.g.*, Appx39 ("The RFIB 2001

Press Release reported that a '14-day course of rifaximin at 550 mg twice-a-day' dosage saw effective results.").

And the district court found that Norwich overcame Salix's evidence of skepticism largely because the RFIB2001 Press Release "was not cited by Quigley, Vanner, or Drossman." Appx42. Fundamentally, the district court concluded, a skilled artisan "would look to the top-line results from the RFIB 2001 Protocol [i.e., the RFIB2001 Press Release] as evidence that rifaximin could be effective in treating IBS-D." Appx43.

The opinion suggests that Salix may have waived any challenge to the RFIB2001 Press Release as prior art by not listing it as disputed in the pretrial order. Appx41. This was incorrect. Salix listed the disputed issues as including "[w]hether Norwich has proven by clear and convincing evidence" that "Harary Reply Report Exhibit C" (another name for the RFIB2001 Press Release) "qualif[ied] as prior art to the Asserted IBS-D Patent claims." Appx1457.

**2. The district court relies on prior art disclosing positive results for dosages well below the claimed dosage.**

The district court found that the prior art "describes positive results from a range of doses," Appx39, but three of the four prior art references credited by the district court (Pimentel 2006, Cuoco, and Barrett) disclosed positive results only for 1,200 mg/day. The fourth—the RFIB2001 Press Release—reported effective results only for 1,100 mg/day (and indicated that the higher dosage tested was ineffective).

The district court did not identify any prior art reporting positive results from treating IBS-D with doses larger than 1,200 mg.

Nonetheless, the district court found that the claimed dosage (1,650 mg/day, nearly 40% larger) was "within the known range," Appx34, and thus reasoned that treating patients using the dosage was "not inventive," Appx39 (quoting *In re Applied Materials, Inc.*, 692 F.3d 1289, 1295 (Fed. Cir. 2012)).

For these reasons, the district court held that the IBS Claims were invalid as obvious. Appx46.

## II. The Polymorph Patents

The district court also held invalid as obvious the asserted claims of the Polymorph Patents, *id.*, which claim a specific form of rifaximin that they label "polymorphic form β," Appx5-6.

### A. Background on Polymorphism

Polymorphism means that a chemical compound can crystallize with different internal structures. Appx5688. "Polymorphism in active pharmaceutical ingredients, API's, is critical . . . since polymorphs can exhibit different physical and/or chemical properties." *Id.* Different polymorphs are distinguished by their measured X-ray powder diffraction (XRPD) peaks. Appx6.

Skilled artisans were baffled by polymorphism, and they remain so today. *See, e.g.*, Appx5617 (Reutzel-Edens paper, from 2003: "[I]t is not yet possible to

predict when materials will crystallize, let alone when multiple crystal forms will appear."); Appx5688 (Vishweshwar paper, from 2005: "Polymorphism, the existence of more than one crystalline form of a compound, is an intensely studied phenomenon, yet it remains poorly understood and controlled."); *see also* Appx3460-3461 (Myerson). Scientists do not "know, based on molecular structure alone, whether a compound will be polymorphic" or whether "all possible polymorphs have been found." Appx5146 (Cruz-Cabeza paper, from 2020); *see also* Appx5589 (Stahly paper, from 2007: "The ability to predict whether a given compound will exist in multiple crystal forms does not yet exist, although not for lack of effort.").

Since polymorphism is an unpredictable art, Appx3434-3436, Appx3440-3441 (Zaworotko); Appx3460-3461, Appx3477 (Myerson), skilled artisans use "polymorph screens"—trial-and-error experiments—to attempt to find new polymorphs or crystalline forms of substance. Appx3462 (Myerson). There is no standard way to perform polymorph screens. Appx3464-3465 (Myerson) (discussing eight techniques); Appx5376-5412; Appx5668-5687. And minor differences among any of the numerous variables used in conducting a screen can have significant effects on how a compound crystallizes. Appx5617 ("[E]ven with the most carefully designed and executed screens, polymorphs . . . are all too frequently discovered by serendipity.").

### B. Alfasigma Discovers a Polymorphic Form of Rifaximin that It Names "Form β"

The rifaximin chemical compound was invented by scientists at Alfa Wassermann, which is now part of Alfasigma, in the early 1980s. Appx2532.

But until the early 2000s, it was unknown that rifaximin is polymorphic, i.e., that rifaximin sometimes crystallizes with different internal structures. Appx3433-3434; Appx3467-3468; Appx3796 ¶ 218.

For example, Cannata, a prior art reference considered by the patent examiner, Appx3466, Appx3475, discloses methods for preparing rifaximin. But it does not discuss polymorphism or identify the crystalline forms (if any) prepared by the examples. Appx3469-3470 (Myerson).

In the early 2000s, a group of Alfasigma scientists noticed differences in different batches of rifaximin. Appx2532. In collaboration with scientists at the University of Bologna, they discovered that rifaximin could exist in different polymorphic forms, with different properties, and determined how to consistently produce particular forms. *Id.*; *see also* Appx85 at 1:41-42 ("It has now been found, unexpectedly, that there are several polymorphous forms [of rifaximin].").

One form of rifaximin identified (and patented) by Alfasigma was a form with "water content higher than 4.5%, preferably between 5.0% and 6.0%," and with an x-ray powder diffractogram showing "peaks at the values of the diffraction angles 20 of 5.4°; 6.49°; 7.0°; 7.80°; 9.09°; 10.49°; 13.10°; 14.40°; 17.10°; 17.90[°];

18.30[°]; 20.99°." Appx87 at 5:65-6:3. They labeled this form "rifaximin β," Appx87 at 5:65, or "rifaximin in polymorphic form β."

The Polymorph Patents, which the other appellants later licensed from Alfasigma, have a priority date of November 7, 2003. Claim 4 of the '199 Patent and Claim 36 of the '206 Patent (the "Polymorph Claims") both claim rifaximin "in polymorphic form β, wherein the rifaximin has x-ray powder diffraction pattern peaks at about 5.4°; 9.0°; and 20.9° 2θ."[6]

### C. The District Court Holds the Polymorph Claims Invalid as Obvious

Although it was undisputed that rifaximin was not known to be polymorphic and rifaximin form β was not known to exist, the district court determined that the Polymorph Claims were invalid as obvious. The district court first found that skilled artisans "would have been motivated to characterize the rifaximin produced by the Cannata processes." Appx13. Had skilled artisans done so, the district court found, they "would have [had] a reasonable expectation of success in characterizing the polymorph β, as opposed to the other forms of rifaximin" because "polymorph β is a commonly produced polymorph and the most stable form of rifaximin." Appx14.

[6] Claim 4 of the '199 Patent adds the requirement that "the rifaximin has a water content of greater than 5%." Claim 36 of the '206 Patent claims "a solid pharmaceutical composition" comprising rifaximin in polymorphic Form β and a "pharmaceutically acceptable excipient or carrier," "wherein the rifaximin Form β has a water content of between about 4.5% to about 40%."

The district court viewed it as irrelevant that a skilled artisan "would not have been able to predict the precise peaks that characterize rifaximin β." Appx14. "[T]he XRPD [x-ray power diffraction] peaks and water content are 'inherent' properties of a crystal form[.]" Appx15. It was irrelevant to the district court that skilled artisans would not have been motivated to create or have expected success in creating the particular form β claimed.

The district court expressly rejected the contrary analysis of a different district court: "Plaintiffs call to my attention *Pharmacyclics LLC v. Alvogen Pine Brook LLC*. I have considered that case but I do not agree with it on this point." Appx15 n.1 (internal citation omitted).

## III. The District Court Enters Judgment

Based on its determinations that the asserted claims of the HE Patents were valid and infringed by Norwich's ANDA, the district court entered judgment in accordance with the Hatch-Waxman Act ordering that the FDA not finally approve ANDA No. 214369 until expiration of the HE Patents in October 2029. Appx51. Six days later, Salix filed a notice of appeal. Appx3965.

Twenty-eight days after entry of judgment, Norwich moved to modify the judgment under Rule 60(b), asking the district court to remove the judgment's "prohibition on FDA's approval" of Norwich's "Amended ANDA" that removed "the HE Indication from the proposed ANDA labeling." Appx3980-3981.

In May 2023, the district court denied Norwich's motion. Appx52. The district court explained that no "changed circumstances" warranted modification of the judgment: "The only changed circumstance is that [Norwich] decided to amend its ANDA . . . nearly one month after the final judgment. The changed circumstance is simply a voluntary decision of the trial loser to change course, which is neither unanticipated nor unforeseeable." Appx53-54. Norwich "fully litigated the merits of its non-infringement and invalidity case, lost, and now seeks a way around the final judgment through Rule 60(b)." Appx55.

Following the district court's denial of Norwich's Rule 60(b) motion, this Court reinstated Salix's appeal. No. 22-2153, Dkt. 19. Norwich filed a notice of appeal of the judgment and the denial of its Rule 60(b) motion. Appx4243. This Court consolidated the appeals and, on June 29, 2023, denied Norwich's request to shorten the briefing schedule. No. 22-2153, Dkt. 27.

## SUMMARY OF THE ARGUMENT

The district court erred in two ways in holding the IBS-D Claims invalid as obvious. First, the district court relied heavily on a reference—the RFIB2001 Press Release—that Norwich failed to prove was prior art. Appx42. To prove that the press release was prior art under pre-AIA Section 102(a), Norwich bore the burden to show by clear-and-convincing evidence that the work was "by others" and not the inventor's work. *Google LLC v. IPA Techs. Inc.*, 34 F.4th 1081, 1085–86 (Fed. Cir. 2022); *Mahurkar v. C.R. Bard, Inc.*, 79 F.3d 1572, 1576 (Fed. Cir. 1996).

Norwich failed to carry its burden. The RFIB2001 Press Release quotes a named inventor discussing the results of "our" study, Appx7480, *see also* Appx3178, and the IBS-D Patents' specifications discuss the underlying study's results.

The district court was wrong to suggest that Salix forfeited this argument. Appx41. In an exhibit to the Joint Pretrial Order, Salix listed whether "Harary Reply Report Exhibit C" constituted prior art as a contested issue. Appx1457. This is another name for the "RFIB2001 Press Release." *E.g.*, Appx1708-1709; Appx1740.

The error was harmful. The RFIB2001 Press Release was the key piece of prior art relied upon by the district court in finding an expectation of success. *See, e.g.*, Appx42 ("Its disclosure of positive results would give a POSA a reasonable expectation of success in using rifaximin to treat IBS-D."). At a minimum, this Court would need to remand for reconsideration.

No remand is necessary, however, because of the second error: even considering the RFIB2001 Press Release, the district court erred in finding a reasonable expectation of success in treating IBS-D using the claimed dosage: 1,650 mg/day.

Norwich was required to show a reasonable expectation of success for the specific rifaximin dosage claimed. *Teva Pharms. USA, Inc. v. Corcept Therapeutics, Inc.*, 18 F.4th 1377, 1381 (Fed. Cir. 2021). The opinion does not find such an expectation expressly. The district court instead relied on this Court's "prior-art-range" cases, which hold that claiming a specific value within a range known to be successful is obvious. Appx39 (citing *In re Applied Materials, Inc.*, 692 F.3d at 1295).

But the highest dosage for which the district court found that the prior art disclosed positive results in treating IBS-D was 1,200 mg/day. *Id.* The RFIB2001 Press Release reported positive results only for 1,100 mg/day, *id.*, and indicated that the higher dosage from the RFIB2001 Protocol (2,200 mg/day) was unsuccessful, Appx3314; Appx3042.

Because the claimed dosage falls outside the range known to be safe and effective, the district court erred in relying on prior-art-range cases. *See Teva*, 18 F4th at 1382–83. This Court should render judgment that Norwich failed to show that the IBS-D Claims are obvious.

The district court also erred in analyzing the Polymorph Claims. The district court found that skilled artisans "would have been motivated to characterize the rifaximin produced by the Cannata processes," Appx13, and that if a skilled artisan had done so, the skilled artisan would have been reasonably likely to characterize "the polymorph β, as opposed to the other forms of rifaximin." Appx14.

The district court expressly rejected (at Appx15 n.1) the contrary analysis of *Pharmacyclics LLC v. Alvogen Pine Brook LLC*, 556 F. Supp. 3d at 412, which this Court subsequently affirmed. No. 21-2270, 2022 WL 16943006 (Fed. Cir. Nov. 15, 2022). *Pharmacyclics* holds that the correct inquiry is whether skilled artisans would be motivated to create (and have an expectation of success in creating) the specific claimed polymorph, with the particular claimed x-ray diffraction peaks. 556 F. Supp. 3d at 412; 2022 WL 16943006, at *10.

Applying the correct legal standard from *Pharmacyclics*, the district court erred in finding a motivation and a reasonable expectation of success in creating the claimed polymorph. This Court should reverse the invalidation of the Polymorph Claims.

## STANDARD OF REVIEW

This Court reviews the district court's findings of fact for clear error and its legal rulings de novo. *Eli Lilly & Co. v. Teva Parenteral Meds., Inc.*, 845 F.3d 1357, 1372 (Fed. Cir. 2017).

Obviousness is a question of law based on underlying factual findings, including the scope and content of prior art. *IXI IP, LLC v. Samsung Elecs. Co., Ltd.*, 903 F.3d 1257, 1262 (Fed. Cir. 2018); *ZUP, LLC v. Nash Mfg., Inc.*, 896 F.3d 1365, 1371 (Fed. Cir. 2018). The allocation of the burden of proof is a legal issue, *Medtronic, Inc. v. Mirowski Family Ventures, LLC*, 571 U.S. 191, 198–99 (2014), which this Court reviews de novo.

To show that a patent is invalid as obvious, an accused infringer must prove by clear and convincing evidence "that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so." *Eli Lilly*, 845 F.3d at 1372 (quoting *Proctor & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009)).

## ARGUMENT

### I. The District Court Erred in Holding the IBS-D Claims Invalid as Obvious.

The district court committed two independent errors in holding the IBS-D Claims invalid as obvious. It relied heavily on the RFIB2001 Press Release, even though Norwich failed to carry its burden to prove that the press release was "by others" as required by pre-AIA Section 102(a). It also held that a skilled artisan would have had a reasonable expectation of success in treating patients with the claimed dosage (1,650 mg/day), even though the highest dosage that the district court found reported by the prior art for the successful treatment of IBS-D was 1,200 mg/day, significantly lower than the claimed dosage. Each of these errors independently requires reversal.

#### A. The District Court Erred by Relying on the RFIB2001 Press Release.

The district court erred by treating the RFIB2001 Press Release as prior art under pre-AIA Section 102(a) because Norwich failed to carry its burden to prove that the press release was "by others."

### 1. Norwich failed to carry its burden to prove that the RFIB2001 Press Release was "a work of others."

#### a. The RFIB2001 Press Release could be prior art only if it was a work of others.

Norwich argued that the RFIB2001 Press Release was prior art under pre-AIA Section 102(a).[7] Appx1708. "[Pre-AIA] Section 102(a) denies any applicant for a patent an exclusive right to any invention already 'known or used by **others** in this country.'" *Invitrogen Corp. v. Biocrest Mfg., L.P.*, 424 F.3d 1374, 1381 (Fed. Cir. 2005). Under this provision, the inventor's "own work is not prior art . . . even though it has been disclosed to the public in a manner or form which otherwise would fall under 102(a)." *In re Katz*, 687 F.2d 450, 454 (C.C.P.A. 1982); *accord Duncan Parking Techs., Inc. v. IPS Grp., Inc.*, 914 F.3d 1347, 1357 (Fed. Cir. 2019) (involving pre-AIA Section 102(e)). An inventor who "has not contributed to the store of knowledge . . . has no entitlement to a patent." *Woodland Tr. v. Flowertree Nursery, Inc.*, 148 F.3d 1368, 1370 (Fed. Cir. 1998). But under Section 102(a), "an inventor's own work cannot be used to invalidate patents protecting his own later inventive activities." *Invitrogen*, 424 F.3d at 1381.

[7] Because the RFIB2001 Press Release was published within one year of the priority date of the IBS-D Patents, it cannot constitute prior art under pre-AIA Section 102(b). *See* Appx33 (February 2008 priority date for the claims); Appx7477 (September 5, 2007 publication of the RFIB2001 Press Release); 35 U.S.C. § 102(b) [pre-AIA] (limiting prior art to publications "more than one year prior to the date of the application").

"Whether a reference is a work of others for the purposes of [pre-AIA] § 102(a) is . . . a question of law based on underlying facts." *Google*, 34 F.4th at 1085 (quoting *Allergan, Inc. v. Apotex Inc.*, 754 F.3d 952, 969 (Fed. Cir. 2014)).

**b. Norwich bore the burden to prove, by clear and convincing evidence, that the RFIB Press Release was prior art.**

The burden of persuasion—the burden to "prove something to a specified degree of certainty"—always remains with the party challenging a patent's validity. *Google*, 34 F.4th at 1085 (quoting *Tech. Licensing Corp. v. Videotek, Inc.*, 545 F.3d 1316, 1326 (Fed. Cir. 2008)). In district court, the challenger bears "the burden of persuasion by clear and convincing evidence on all issues relating to the status of [a reference] as prior art." *Mahurkar*, 79 F.3d at 1576.

The patent challenger thus bears the burden to establish that a reference was prior art "by others" under pre-AIA Section 102(a). *See Google*, 34 F.4th at 1087–88 (inter partes review); *see also Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1379 (Fed. Cir. 2015) ("[T]he different evidentiary standard in an inter partes review does not alter the shifting burdens between the parties[.]").

Norwich bore the burden to demonstrate—by clear and convincing evidence—that the work reported in the RFIB2001 Press Release was the work of others. *See LSI Corp. v. Regents of Univ. of Minn.*, 43 F.4th 1349, 1356 (Fed. Cir.

2022) ("Tsang's summary of, and reliance on, the earlier work of Dr. Moon and Dr. Brickner does not make Tsang an inventor of the earlier work.").

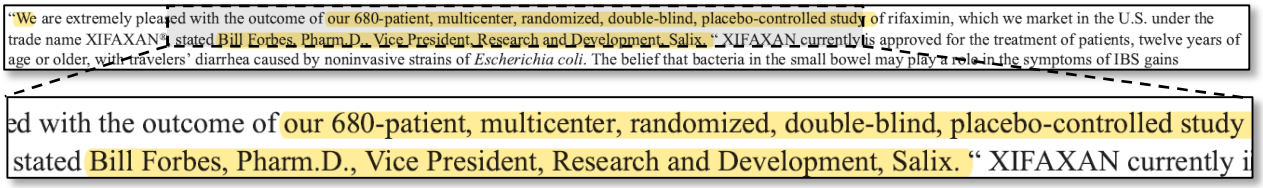
The district court committed legal error and misplaced the burden by asking whether there was "evidence upon which to make a factual finding that the press release was derived from the inventor's work." Appx41. In suggesting that Salix bore the burden of proof, the district court relied on language from *Allergan, Inc. v. Apotex Inc.*, but unlike this case, *Allergan* involved references that appeared on their face to be the work of others: "a publication by Drs. Sherwood and Brandt" and "a publication by Drs. Brandt, VanDenburgh (a named inventor . . . ), Chen, and Whitcup." 754 F.3d at 967.[8] *Google*, which cited *Allergan*, held unequivocally that the challenger bears the ultimate burden to prove that a "reference was prior art 'by another.'" 34 F.4th at 1086. The correct inquiry was whether Norwich proved, by clear and convincing evidence, that the press release was "by others" and not derived from the inventors' work.

[8] In *Allergan*, the face of the references indicated that the references were the work of others, and no evidence supported a contrary finding. *See* 754 F.3d at 969 ("[W]hether Dr. VanDenburgh supervised the logistics of the clinical trial on her own or not, appellees have not produced evidence that shows she was responsible for directing the production of either article's content, which includes the design, trial, and analysis of results. There is no evidence, therefore, that appellees' explanation of the Brandt references is in any way consistent with the content of the articles and the nature of the publications.").

### c. Norwich failed to satisfy its burden of persuasion.

Norwich failed to satisfy its burden. Norwich made no attempt to show that the RFIB2001 Press Release described the work of "others." The only evidence introduced at trial links the RFIB2001 Press Release (and the underlying RFIB2001 study) to the IBS-D Patents.

The press release quotes Dr. Bill Forbes discussing "our" study.


"We are extremely pleased with the outcome of our 680-patient, multicenter, randomized, double-blind, placebo-controlled study of rifaximin, which we market in the U.S. under the trade name XIFAXAN®," stated Bill Forbes, Pharm.D., Vice President, Research and Development, Salix. "XIFAXAN currently is approved for the treatment of patients, twelve years of age or older, with travelers' diarrhea caused by noninvasive strains of *Escherichia coli*. The belief that bacteria in the small bowel may play a role in the symptoms of IBS gains

ed with the outcome of our 680-patient, multicenter, randomized, double-blind, placebo-controlled study
stated Bill Forbes, Pharm.D., Vice President, Research and Development, Salix. " XIFAXAN currently i

Appx7480. Norwich's expert, Dr. Harary, testified that Dr. Forbes is both an inventor of the IBS-D patents and the speaker in the RFIB2001 Press Release:

> Q. . . . Do you recognize the name of who's being quoted?
>
> A. Yes, Bill Forbes was one of the officers of Salix, is being quoted.
>
> Q. And do you recall whether Dr. Forbes is a named inventor of the '569 patent?
>
> A. Yes.
>
> Q. Do you recall whether he's a named inventor of the '667 patent?
>
> A. I think he is also, yes.

Appx3178. Norwich made similar representations in exhibits to the Joint Pretrial Order. *See* Appx1709 (acknowledging that the press release quotes "Named inventor Bill Forbes").

The IBS-D Patents discuss the RFIB2001 study—on which the RFIB2001 Press Release reports—at length. Figures 1, 2, and 4-6 of the '569 Patent bear the

label "RFIB2001," Appx103-104, Appx106-108, and Norwich's expert confirmed that Figure 3 showed a schematic of the RFIB2001 study design, Appx3244-3243. Example 1 of the IBS-D Patents discusses the same 680-patient study discussed in the RFIB2001 Press Release. *See* Appx119-121, '569 Patent at 21:65-25:52 (discussing RFIB2001 study and results); Appx151-153, '667 Patent at 23:63-27:56 (same).

The only evidence presented at trial thus indicated that the RFIB2001 study (for which the RFIB2001 Press Release reported high-level results) was part of the basis for the IBS-D Patents, not work "by others" that can be used to invalidate these patents under Section 102(a). No evidence in the record permits the finding that the RFIB2001 Press Release was work "by others." Because Norwich failed to satisfy its burden, the district court erred in relying on the RFIB2001 Press Release as prior art.

**2. The district court was incorrect to suggest that Salix waived its challenge to the RFIB2001 Press Release as prior art.**

The district court suggested—although it did not find—that Salix waived any challenge to whether the RFIB2001 Press Release constitutes prior art. Appx41. This is incorrect: Salix preserved this argument.

The district court appears to have been confused by the parties' use of different designations to refer to the same document. *See* Appx41 ("I see a list of items the prior art status of which Plaintiffs contest, which does not include the press

release (*id.* at 6 ¶ 28)[.]"). In Paragraph 28 of Exhibit 2 to the Joint Pretrial Order, Salix listed "Harary Reply Report Exhibit C" as contested prior art:

> 28. Whether Norwich has proven by clear and convincing evidence that the following qualify as prior art to the Asserted IBS-D Patent claims:
>
> - Harary Opening Report Exhibit E;
> - Pimentel Exhibit 9, and what Norwich refers to as "prior art use by Glass;"
> - Harary Reply Report Exhibit C;

Appx1457 (emphases added). "Harary Reply Report Exhibit C" refers to the "RFIB2001 Press Release." Other exhibits to the Joint Pretrial Order make this clear.

> **iv. Salix's September 5, 2007 Press Release**
>
> 855. On September 5, 2007, Salix issued a press release announcing the successful completion of its Phase IIb trial to assess the efficacy and safety of rifaximin in the treatment of patients with IBS-D. (Harary Reply Ex. C.) This press release was published before the earliest claimed filing date for the '569 and '667 patents. Accordingly, it is prior art under 35 U.S.C. § 102(a).

Appx1708 (emphasis added); *see also* Appx1740 ("Salix Press Release, dated Sep. 5, 2007, at 1 (Harary Reply Ex. C at Ex. 99.2)"); Appx1745 (citing "Harary Reply Report Ex. C" for the proposition that a skilled artisan would have known "the

topline results of the RFIB 2001 Study"); Appx1750 (same for knowing that the "RFIB 2001 Study achieved 'adequate relief' of symptoms").[9]

Salix thus listed whether the "RFIB2001 Press Release" (i.e., "Harary Reply Report Exhibit C") constituted prior art as a disputed issue in the pretrial order. Appx1457. Under regional circuit law, pretrial orders "are to be liberally construed to embrace all legal and factual theories inherent in the issues defined therein." *U.S. Gypsum Co. v. Schiavo Bros., Inc.*, 668 F.2d 172, 181 n.12 (3d Cir. 1981). And in its proposed findings of fact and conclusions of law and its post-trial briefing, Salix explained that Norwich failed to satisfy its burden to prove that the press release was prior art. *See* Appx3787 ¶ 183; Appx3744. Salix fully preserved the argument that the RFIB2001 Press Release was not prior art.

**3. The error in treating the RFIB2001 Press Release as prior art was harmful.**

The RFIB2001 Press Release was the critical piece of evidence the district court relied upon in invalidating the IBS-D Claims. Most of the prior art consisted of retrospective chart reviews—the "lowest level of [medical] evidence," Appx3256, and which do not control for the placebo effect—but the RFIB2001 Press Release disclosed the results of a scientific, randomized, double-blind, placebo-controlled

[9] The RFIB2001 Press Release is also not among the undisputed prior art in the pretrial order. *See* Appx1444-1447.

study, Appx7480-7482, "the gold standard" to test a treatment for IBS-D, Appx6403.

Given its reliability (particularly compared to that of other references), it is unsurprising that the district court relied on the RFIB2001 Press release so heavily in its opinion:

- "As of the priority date, a POSA would have known about the successful RFIB 2001 Protocol results."
- "Rifaximin had been shown to be effective in treating IBS in Pimentel 2006 and IBS-D in the RFIB 2001 Protocol[.]"
- "The RFIB 2001 Press Release reported that a '14-day course of rifaximin at 550 mg twice-a-day' dosage saw effective results."
- "[The RFIB2001 Press Release's] disclosure of positive results would give a POSA a reasonable expectation of success in using rifaximin to treat IBS-D."
- "More importantly, a POSA would look to the top-line results from the RFIB 2001 Protocol [i.e., the RFIB2001 Press Release] as evidence that rifaximin could be effective in treating IBS-D[.]"

Appx38-43.

The district court placed particular emphasis on the RFIB2001 Press Release in overcoming the evidence of skepticism. Three articles published shortly before the IBS-D Patents reviewed the literature—including the majority of the prior art cited by Norwich—and concluded that rifaximin had not been shown to be successful in treating IBS-D. Appx42. In discounting this evidence, the district court relied on the fact that these articles did not cite the RFIB2001 Press Release.

*See* Appx44 ("Norwich argues that one of the [skeptical] articles was published before Yang and the RFIB 2001 Press Release, and the other two articles did not cite those references."); Appx42 (noting that the "RFIB 2001 Press Release . . . was not cited by Quigley, Vanner, or Drossman," skeptical literature).

Because of the district court's erroneous reliance on the RFIB2001 Press Release in finding an expectation of success, this Court should, at a minimum, vacate the obviousness determination and remand. *See, e.g., Riverwood Int'l Corp. v. R.A. Jones & Co.*, 324 F.3d 1346, 1357 (Fed. Cir. 2003); *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.*, 796 F.2d 443, 449 (Fed. Cir. 1986).

### B. The District Court Erred in Finding that a Skilled Artisan Would Have Had an Expectation of Success in Using the Claimed Dosage—1,650 mg/day—to Treat IBS-D.

Remand is unnecessary, however, because even considering the RFIB2001 Press Release, the district court erred in finding that a skilled artisan would have had a reasonable expectation of success in using the claimed dosage—1,650 mg/day—to treat IBS-D. This argument applies to all three combinations of prior art, and this Court need not remand because "the record permits only one resolution of the factual issue." *Pullman-Standard v. Swint*, 456 U.S. 273, 292 (1982).

When a patent claims a method of treatment using a specific dosage, the reasonable-expectation-of-success analysis must focus on the specific dosage claimed. *Teva*, 18 F.4th at 1381 (holding that the patent challenger was required "to

show a reasonable expectation of success for a specific mifepristone dosage [claimed]"). Norwich was thus required to prove a reasonable expectation of success for the specific rifaximin dosage claimed: 1,650 mg/day (550 mg three times/day).

But the IBS-D Patents claim a dosage significantly (nearly 40%) outside the range for which the prior art disclosed positive results in treating IBS-D. The highest dosage for which the district court found that the prior art disclosed positive results was 1,200 mg/day, far less than the claimed 1,650 mg/day. Because the claimed dosage was outside the range known to be effective in treating IBS-D and the district court relied only on the "known range" for a reasonable expectation of success in using the claimed dosage to treat IBS-D, the district court erred in finding a reasonable expectation of success.

**1. The claimed daily dose (1,650 mg) is nearly 40% larger than the largest daily dose reported to be successful in the prior art (1,200 mg).**

The opinion states that "the prior art disclosed positive results in using rifaximin to treat IBS-D for a range of doses" and that the IBS-D Claims "describe a dosing regimen within the known range." Appx34.

The opinion thus implies—without actually stating—that the "known range" means the range of doses for which "the prior art disclosed positive results." The implication is incorrect: the "positive results" found by the district court all involved dosages far less than the claimed 1,650 mg/day dosage. Three references disclosed

positive results for 1,200 mg/day (Pimentel 2006[10], Cuoco, and Barrett). One disclosed positive results for 1,100 mg/day (RFIB2001 Press Release).

> I also find that a POSA would have had the motivation to select an optimal dosing regimen from within the known range. The prior art describes positive results from a range of doses. **Pimentel 2006 used 400 mg of rifaximin TID** for 10 days and reported "global improvement in IBS." **Cuoco disclosed a total dose of 1200 mg** for 14 days and reported significant reduction in the number of patients having IBS symptoms. **Barrett disclosed 400 mg TID** for 1-5 months. In 2007, Quigley explained, "Antibiotic dose and duration of therapy have not been established. All studies to date have used different doses and antibiotic regimens; the optimal approach needs to be established in a prospective, placebo-controlled, dose-ranging study." The RFIB 2001 Protocol taught a range from 1100 mg to 2200 mg per day for 10-14 days. **The RFIB 2001 Press Release reported that a "14-day course of rifaximin at 550 mg twice-a-day"** dosage saw effective results.

Appx39 (emphases added; internal citations omitted). The claimed dosage (1,650 mg/day) is nearly 40% higher than the highest dosage for which the district court found that the prior art reported positive results (1,200 mg/day).[11]

The opinion discusses only a single dosage in the prior art exceeding 1,650 mg/day: the RFIB2001 Protocol tested "2200 mg per day for 10-14 days." Appx39. But the RFIB2001 Protocol is simply a "protocol that doesn't have any

[10] Pimentel 2006 used 1,200 mg/day for 10 days and failed to significantly improve "hallmark symptoms" of IBS-D (i.e., abdominal pain and diarrhea). *See* Appx4643; Appx5152; Appx3285.

[11] Although not mentioned in this paragraph, the district court also appeared to credit "Yang," Appx7590, a retrospective chart review published by a member of the Cedars-Sinai group, as disclosing positive results in treating IBS-D. Like Pimentel 2006, Barrett, and Cuoco, Yang involved 1,200 mg/day. Appx7592.

results in it." Appx3219. The district court was correct not to find that the RFIB2001 Protocol "describes positive results" for treating IBS-D with rifaximin. *See also Sanofi-Aventis U.S. LLC v. Sandoz, Inc.*, No. CV 20-804-RGA, 2023 WL 4175334, at *14 (D. Del. June 26, 2023) (Andrews, J.) ("I also do not think that the mere existence of a Phase III trial, with no information about its results, would have lifted a POSA's hopes over the bar for a reasonable expectation of success.").

The alternative—treating the disclosure of a study protocol as the equivalent of disclosing positive results for the study—would have dangerous consequences. The RFIB2001 Protocol was available because it was published on "the clinicaltrials.gov archive, which is a government-sponsored archive that shows studies that are ongoing or complete." Appx3173. Federal regulations require these publications, 42 C.F.R. § 11.22, which benefit the public. Companies should not risk losing their future patent rights for making disclosures—particularly disclosures of studies without results—that federal law requires.[12]

[12] This Court distinguishes between obviousness in conducting an experiment and a reasonable expectation of success. *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1070 (Fed. Cir. 2012) ("While it may have been obvious to experiment with the use of the same PK profile when contemplating an extended-release formulation, there is nothing to indicate that a skilled artisan would have had a reasonable expectation that such an experiment would succeed in being therapeutically effective.").

No precedential decision of this Court has treated a clinical trial protocol as evidence—much less sufficient evidence—of an expectation of success. *Vanda Pharmaceuticals Inc. v. Teva Pharmaceuticals USA, Inc.*, involved a Phase III—not

The district court correctly recognized that the only "positive results" associated with the RFIB2001 Protocol were disclosed by the RFIB2001 Press Release. But critically, the RFIB2001 Press Release did not report positive results for the entire dosage range (including 2,200 mg/day) tested in the RFIB2001 study. It reported positive results only for 1,100 mg/day, a "14-day course of rifaximin at 550 mg twice-a-day." Appx7480.

The RFIB2001 Press Release not only fails to disclose positive results for 2,200 mg/day, but skilled artisans would understand it to report negative results for that dosage. *See* Appx3314 ("[I]f the other dosages met the primary endpoint [i.e., succeeded], you would have identified that as well in the press release."). And in fact, the 2,200 mg/day dosage "did not achieve more responders compared to the placebo for adequate relief." Appx3042.

The highest dosage for which the district court found that prior art disclosed positive results was 1,200 mg/day. The claimed dosage—1,650 mg/day—was, at most, within the experimental range (as indicated by the RFIB2001 Protocol) but was outside the range for which the prior art disclosed positive results.

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a Phase II—trial that the district court found "would also have contributed to a skilled artisan's expectation of success." No. 23-1247, 2023 WL 3335538, at *4 (Fed. Cir. May 10, 2023). No similar finding was made regarding the Phase II clinical trial at issue here, and in *Vanda*, the district court relied on the Phase III trial as only "one piece of evidence" regarding expectation of success and "did not find that Vanda's ongoing clinical trial would have given a POSA an expectation of success in using" the claimed dosage. *Id.*

### 2. The district court misapplied this Court's prior-art-range precedent.

Because the claimed dosage fell outside the range known to be successful, the district court erred by applying this Court's prior-art-range cases. Under this Court's precedent, claiming a particular value within a range that is known to be successful is ordinarily not inventive. Appx39 (citing *In re Applied Materials, Inc.*, 692 F.3d at 1295). The "known range" means the range known to work.

Where a claimed dosage is outside the range known to be safe and effective, the "known range" does not render it obvious. In *Teva Pharmaceuticals v. Corcept Therapeutics*, the prior art created an expectation of success for up to 300 mg but not for the claimed 600 mg. 18 F.4th at 1380. "Because there was no expectation of success for any dosage over 300 mg per day, there was no expectation of success for the specific 600 mg per day dosage." *Id.* at 1381. This Court explained that "prior-art-range" cases (such as *Applied Materials*) did not apply because "the general working conditions disclosed in the prior art did not encompass the claimed invention, i.e., there was no overlap in ranges." *Id.* at 1382. Even "if the prior art directed a skilled artisan to try" co-administering a 600 mg per day dosage, "without showing a reasonable expectation of success, Teva did not prove obviousness." *Id.* at 1383.

The analysis of the IBS-D Claims should track *Teva*. As in *Teva*, Norwich was required to prove (here, by clear and convincing evidence) a reasonable

expectation of success in the specific invention claimed: a 1,650 mg/day dosage. As in *Teva*, the expectation of success in using a significantly lower dosage (here, 1,200 mg/day) would not create an expectation of success in using the higher claimed dosage. And as in *Teva*, even if the prior art suggested trying the claimed 1,650 mg/day dosage, without showing a reasonable expectation of success, Norwich failed to prove obviousness.

This Court's other method-of-treatment cases are consistent with *Teva*: where a claimed dosage falls outside the range known to be safe and effective, the "known range" does not render the claimed dosage obvious. *See, e.g.*, *Endo Pharms. Sols., Inc. v. Custopharm Inc.*, 894 F.3d 1374 (Fed. Cir. 2018) (claimed 750 mg dose not obvious in light of known 1000 mg dose); *Ferring B.V. v. Watson Lab'ys, Inc.-Fla.*, 764 F.3d 1401 (Fed. Cir. 2014) (claimed 650 mg dose not obvious in light of known 500 mg dose).[13]

In contrast, a claimed dosage is ordinarily obvious when it falls within a range known to be safe and effective (or is equivalent to a dosage known to be safe and effective). *Yeda Research v. Mylan Pharmaceuticals, Inc.*, 906 F.3d 1031 (Fed. Cir.

[13] *See also In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d at 1072 (claimed "Cmax range of about 80% to 125% of about 20 ng/ml" not obvious in light of known Cmax of "129.5% of 20 ng/ml"); *see also id.* ("The district court, however, cited no evidence specifically indicating that a cyclobenzaprine PK profile with a Cmax of 129.5% of 20 ng/ml would be expected to yield the same therapeutic effect as that with a Cmax range of about 80% to 125% of about 20 ng/ml.").

2018), is a perfect example. There, the dosages known to be safe and effective were: 20 mg daily; 20 mg every other day; 40 mg daily; and 40 mg every other day.[14] *Id.* at 1045. The claimed dosage—40 mg three times per week—fit squarely within the known range, *id.* at 1044, and because the range was known to be successful, skilled artisans would have a reasonable expectation of success in using the claimed dosage. *See also id.* at 1039 ("[C]ombining a 40mg dose with three-times-a-week administration produced a weekly dose virtually identical to the FDA-approved regimen of 20mg GA daily.").

This Court's other decisions are consistent. *See, e.g.*, *Adapt Pharma Operations Ltd. v. Teva Pharms. USA, Inc.*, 25 F.4th 1354, 1368 (Fed. Cir. 2022) (finding obvious a claimed 4mg intranasal dose that "would be bioequivalent to the FDA-approved 1mg injectable dose"); *Boehringer Ingelheim Pharms. Inc. v. Mylan Pharms. Inc.*, 803 F. App'x 397, 402 (Fed. Cir. 2020) (claimed 2.5 or 5 mg doses were within the 1-100 mg range disclosed in an earlier patent); *Hoffmann-La Roche Inc. v. Apotex Inc.*, 748 F.3d 1326, 1332 (Fed. Cir. 2014) (skilled artisans would know that the claimed 150 mg/month was equivalent to the known 5 mg/day).

[14] *See Yeda*, 906 F.3d at 1036 ("FDA approved . . . 20mg GA injected daily"); *id.* ("20mg of GA administered every other day . . . is safe, well tolerated, and probably as effective"); *id.* at 1038 ("daily administration of 40mg GA was effective, safe, and well tolerated"); *id.* at 1037 ("a 40mg GA, every other day dosing regimen . . . is well tolerated and can improve the treatment").

This principle makes sense: if a range of dosages is known to be successful, then a skilled artisan would, ordinarily, have an expectation of success in using any dosage within the range. But merely knowing that a dosage is possible to try (like 2,200 mg/day in the RFIB2001 Protocol) does not create an expectation of success.

Even if skilled artisans would have had a reasonable expectation of success in using between 1,100 mg/day and 1,200 mg/day of rifaximin to treat IBS-D, none of the evidence credited by the district court supports the conclusion that skilled artisans would have a reasonable expectation of success in treating IBS-D using the claimed dosage (1,650 mg/day). The district court erred legally by applying the prior-art-range cases to a dosage outside the range known to be safe and effective. Alternatively, the district court clearly erred by finding that a dosage range up to 2,200 mg/day was known to be safe and effective for treating IBS-D with rifaximin.

**3. This Court should render judgment in favor of Salix.**

Because the claimed 1,650 mg/day was outside the dosage range known to be safe and effective for treatment of IBS-D, the district court clearly erred in finding that a skilled artisan would have had a reasonable expectation of success in treating IBS-D with the claimed dosage.

This Court should reverse the determination that the IBS-D Claims are invalid as obvious and render judgment that Norwich has failed to establish invalidity under any of the three combinations it raised. Although the district court specifically held

the IBS-D Patents invalid as obvious under the combination of Pimentel 2006 and the RFIB2001 Protocol, its analysis of expectation of success in the claimed dosage did not depend on the particular combination. Appx39. In analyzing the "known range," the district court considered both pieces of prior art involved in Norwich's other two combinations (Cuoco and Barrett). *Id.* Like Pimentel 2006, both Cuoco and Barrett reported positive results only for 1,200 mg/day. Neither supports finding an expectation of success in using the higher claimed dosage.

No matter which of Norwich's three combinations is considered, finding that a skilled artisan would have had a reasonable expectation of success treating IBS-D with 1,650 mg/day of rifaximin for 14 days would constitute clear error. Because "the record permits only one resolution of the factual issue," remand to address the other combinations is unnecessary. *Pullman-Standard*, 456 U.S. at 290–91.

This Court should reverse the determination that the IBS-D Claims are obvious, render judgment that they are valid, and order that the FDA not approve Norwich's application until at least after expiration of the IBS-D Patents. In the alternative, if necessary, this Court should remand to the district court.

## II. The District Court Erred in Holding the Polymorph Claims Invalid as Obvious.

The district court also erred in finding the Polymorph Claims invalid as obvious. Specifically, the district court erred in finding that a skilled artisan would

have had a motivation and reasonable expectation of success in combining the Cannata reference with common knowledge to arrive at the claimed polymorph β.

The district court erroneously conflated actual success and the expectation of success. The heart of its analysis was the finding that "polymorph β is a commonly produced polymorph and the most stable form of rifaximin." Appx14. But this (undisputed) fact merely shows that skilled artisans **actually succeed** in producing rifaximin polymorph β. It does not support the conclusion that, at the time of the Polymorph Patents, skilled artisans would have **expected to succeed** in producing the specific form of rifaximin with particular x-ray diffraction peaks that the Polymorph Patents label "polymorph β." This Court held as much in *Pharmacyclics LLC v. Alvogen, Inc.*, No. 21-2270, 2022 WL 16943006 (Fed. Cir. Nov. 15, 2022), and it should follow that decision here.

### A. *Pharmacyclics* and *Grunenthal* Explain How to Analyze the Obviousness of Polymorph Claims.

After the district court's decision, this Court addressed the question at issue here: how to evaluate whether a claim directed to a specific polymorph is obvious in view of the prior art. *Pharmacyclics*, 2022 WL 16943006.

In *Pharmacyclics*, the prior art taught both the chemical structure of the drug compound ibrutinib and that ibrutinib "may be in various forms, including crystalline forms," although it "d[id] not assert that any crystalline forms of ibrutinib actually exist." *Id.* at *5 (internal quotation marks omitted). Other references

described crystalline forms generally and explained how to screen for polymorphs. *See id.* at *6.

The *Pharmacyclics* district court found that although a skilled artisan "would have been motivated to develop **a** crystalline form of ibrutinib" based on the prior art, none of those references "would have motivated an artisan to develop a crystalline form of ibrutinib with the claimed 2-Theta peaks" (what the *Pharmacyclics* patents labeled "Form A"). 556 F. Supp. 3d at 412. The district court based that finding on the fact that "[d]iscovering new crystalline forms is challenging and unpredictable." *Id.* at 410.

This Court affirmed:

> [T]he [district] court found that, given the lack of teaching in the art regarding crystalline forms of ibrutinib and the expert testimony that polymorph screening can produce unpredictable results, **a skilled artisan would not have reasonably expected success in producing Form A** of ibrutinib. That finding was not clearly erroneous.
>
> [Therefore] we hold that the district court did not err in finding that a skilled artisan would not have been motivated to combine the prior art to create Form A and would not have had a reasonable expectation of success in doing so[.]

2022 WL 16943006, at *10–11 (citation omitted; emphasis added).

In *Pharmacyclics*, this Court relied on *Grunenthal GMBH v. Alkem Lab'ys Ltd.*, 919 F.3d 1333, 1344 (Fed. Cir. 2019), the only other case where this Court has directly addressed polymorph obviousness. *Grunenthal* affirmed a finding that a skilled artisan would not have expected success in producing a particular crystalline

form when a skilled artisan would not have "know[n] how the multiple variables involved in conducting a polymorph screen would affect the recrystallization" of the compound. *Id.* at 1343 ("Because the record indicates that there was (1) no known or expected polymorphism of tapentadol; (2) no evidence that the synthesis of Example 25 results in any Form A; and (3) no guidance as to what particular solvents, temperatures, agitation rates, etc., were likely to result in Form A, Alkem failed to prove that a POSA would have reasonably expected a polymorph screening of the Form B disclosed in the '737 patent to result in Form A.").

*Pharmacyclics* and *Grunenthal* make clear that challengers to polymorph claims must prove (by clear and convincing evidence) that skilled artisans would have had a motivation and a reasonable expectation of success in developing the specific claimed polymorph (i.e., the form with the specific claimed x-ray diffraction peaks), not just motivation and expectation of success to look for polymorphs. *See also Bristol-Myers Co. v. U.S. Int'l Trade Comm'n*, 892 F.2d 1050 (Table), 1989 WL 147230, at *4 (Fed. Cir. 1989) (citing older Court of Custom and Patent Appeals decisions for the proposition that "[t]here must be a suggestion or teaching in the prior art that the [a particular] crystal structure could or should be made" to render a crystalline structure obvious).

### B. Cannata and Common Knowledge Did Not Provide Skilled Artisans with a Motivation and Reasonable Expectation of Success in Creating the Claimed β Polymorph.

The Polymorph Claims both claim a form of rifaximin that "has x-ray powder diffraction pattern peaks at about 5.4°; 9.0°; and 20.9° 2θ," which these patents label "polymorphic form β." *See generally* Appx85 at 1:47-48 (explaining that the polymorphic forms are labeled "on the basis of their respective specific diffractograms"). To establish that these claims are invalid as obvious, Norwich needed to prove by clear and convincing evidence that skilled artisans would have had a reasonable expectation of success in developing the specific claimed polymorphic form β, a form of rifaximin with the specific claimed x-ray diffraction peaks. *Pharmacyclics*, 2022 WL 16943006, at *10 ("[A] skilled artisan would not have reasonably expected success in producing Form A of ibrutinib.").

The district court correctly found that "rifaximin's polymorphism was unknown as of the priority date." Appx13. In other words, skilled artisans did not even know that rifaximin had different crystalline forms. Nor were any specific forms known: "[N]o rifaximin had been publicly characterized as a particular form as of the priority date." Appx13. Salix's expert, Dr. Myerson, explained that a skilled artisan "would not have been able to predict in advance the existence of any

crystalline forms, nor could they predict their properties." Appx3459. No contrary evidence was introduced (much less credited by the district court).[15]

Just as he testified in *Pharmacyclics*, 556 F. Supp. 3d at 410, Dr. Myerson testified in this case that there is no standard way of conducting a polymorph screen (the set of experiments to attempt to find new polymorphs). Appx3462-3463. Any number of variables "are well known to influence what polymorphs can form." Appx3463.

None of the prior art describes a particular crystalline form of rifaximin or provides any guidance to a skilled artisan on how to make a particular crystalline form of rifaximin. Appx3477. Cannata (which was considered by the patent examiner, Appx3466, Appx3475) discloses only general methods for preparing rifaximin, not anything about rifaximin's different forms:

> Q. [W]hat does Cannata disclose about rifaximin being polymorphic?
>
> A. It does not disclose anything about it being polymorphic.
>
> Q. And what does Cannata disclose about rifaximin Beta?
>
> A. It does not discuss rifaximin Beta.

[15] "It's not yet possible to predict when materials will crystallize, let alone when multiple crystal forms will appear. . . . The ability to predict whether a given compound will exist in multiple crystal forms does not yet exist[.]" Appx3460 (describing papers); *see also* Appx3434-3436, Appx3440-3441; Appx3460-3461, Appx3477 (Myerson). It is "extremely not possible to predict what, if any, polymorphs you will get or what their properties will be." Appx3461.

Appx3469; *see also* Appx3469-3470; *see also* Appx3391 ("Does Cannata disclose rifaximin beta? A. Not expressly[.]"); Appx4526 (Cannata).

The Viscomi Declaration, Appx4846, on which the district court relied, cannot fill in any missing holes. The Viscomi Declaration states that only some batches of rifaximin prepared according to Cannata yielded rifaximin form β. *Id*. But the 2006 Viscomi Declaration post-dates the 2003 priority date of the Polymorph Patents. The Viscomi Declaration cannot show that a skilled artisan would have had an expectation of success in 2003. *Cf. Yeda*, 906 F.3d at 1037–41 (discussing the admissibility of non-prior art only for their "proper supporting roles" such as indicating the level of ordinary skill in the art).

Like the district court, Norwich's expert Dr. Zaworotko also solely relied on the Viscomi Declaration and identified no prior art supporting his opinion that a skilled artisan would have known about form β, let alone understand that "β is the most stable form" at the time of the invention. Appx14.

Under this Court's precedent, there was no motivation or expectation of success to create rifaximin in polymorphic form β (i.e., the form in which rifaximin has x-ray powder diffraction pattern peaks at about 5.4°; 9.0°; and 20.9° 2θ). *Pharmacyclics*, 2022 WL 16943006 at *10; *see also Grunenthal*, 919 F.3d at 1341 (affirming the conclusion that a polymorph was nonobvious because the challenger failed "to prove a reasonable expectation of success in arriving at Form A").

Dr. Myerson captured the facts perfectly:

> [A] POSA would not have a reasonable expectation of success in finding rifaximin Beta with the claimed x-ray diffraction peaks and water content because they couldn't have predicted in advance it existed with those properties.

Appx3477-3478. Put simply, "[Y]ou can't have a reasonable expectation of success to find something you don't know exists." Appx3478. *See Pharmacyclics*, 556 F. Supp. 3d at 412 ("As the prior art did not teach how to make any crystalline form of ibrutinib, an artisan of ordinary skill in June 2012 could not reasonably have expected to make a crystalline form of ibrutinib with the six claimed 2-Theta peaks.").

### C. The District Court Applied the Wrong Test.

Rather than follow the polymorph obviousness analysis from the *Pharmacyclics* district court opinion, the district court here expressly parted ways with the decision:

> Plaintiffs call to my attention *Pharmacyclics LLC v. Alvogen Pine Brook LLC*. I have considered that case but I do not agree with it on this point.

Appx15 n.1 (internal citations omitted).

The district court—without the benefit of this Court's subsequent affirmance of *Pharmacyclics*—thought it sufficient that "a POSA would have been motivated to characterize the rifaximin produced by the Cannata processes," Appx13, and that if a skilled artisan had done so, the skilled artisan would have been reasonably likely

to characterize "the polymorph β, as opposed to the other forms of rifaximin." Appx14. It was irrelevant to the district court that a skilled artisan could not have predicted "the precise peaks that characterize rifaximin β." Appx14.

The district court applied the approach to polymorph obviousness rejected in *Pharmacyclics*. As here, the *Pharmacyclics* district court found that "an artisan of ordinary skill would have been motivated to develop **a** crystalline form" of the compound. 556 F. Supp. 3d. at 412. But the *Pharmacyclics* district court correctly recognized that "the inquiry is not whether an artisan would have been motivated to develop **a** crystalline form of ibrutinib; the inquiry is whether an artisan would have been motivated to develop crystalline ibrutinib having [the specific claimed peaks]." *Id*. On appeal, this Court agreed that the "motivat[ion] to develop **a** crystalline form" was insufficient, 2022 WL 16943006, at *10, and that the proper inquiry was whether a skilled artisan would "have been motivated to combine the prior art to create [the claimed] Form A," *id.* at *11.

The *Pharmacyclics* district court's analysis of expectation of success similarly focused on the specific claimed polymorph, asking whether a skilled artisan could "reasonably have expected to make a crystalline form of ibrutinib with the six claimed 2-Theta peaks." 556 F. Supp. 3d at 412. Again, this Court agreed, affirming based on the finding that "a skilled artisan would not have reasonably expected success in producing Form A of ibrutinib." 2022 WL 16943006, at *10.

The correct inquiry is whether a skilled artisan would have been motivated to make and had a reasonable expectation of success in making a crystalline form of rifaximin with the claimed peaks. Particularly in light of the finding that the polymorphic nature of rifaximin was unknown at the time of the patents, the district court clearly erred in a finding of motivation and expectation of success in creating the claimed form of rifaximin, which the patents label "form β."[16] *See generally Bristol-Myers*, 1989 WL 147230, at *6 ("There must be an affirmative suggestion or teaching in the prior art whereby it would have been obvious to make the new [form]; not simply the absence of obstacle. No such suggestion or teaching has been shown.").

* * *

There is no principled basis to reach a different result here than in *Pharmacyclics*, which considered a similar factual record and found that there was no motivation to make and no reasonable expectation of success in making the specific polymorphs claimed. The district court clearly erred in finding otherwise.

[16] The district court relied on *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1365 (Fed. Cir. 2007), and *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006), in analyzing reasonable expectation of success. Appx14. Neither is a polymorph case, and both provide only general, broad statements about the law not requiring certainty of success. *Grunenthal* and *Pharmacyclics* are more on point.

## CONCLUSION & PRAYER FOR RELIEF

The dosage claimed in the IBS-D Claims (1,650 mg/day) is outside the dosage range known to be safe and effective, and no evidence credited by the district court supported finding that a skilled artisan would have had a reasonable expectation of success in treating IBS-D with the claimed dosage. This Court should reverse the district court's judgement that the IBS-D Claims are invalid, render judgment that Norwich failed to show invalidity, and order the FDA not to approve Norwich's ANDA until at least the expiration of the IBS-D Patents.

In the alternative, because the district court erroneously treated the RFIB2001 Press Release as prior art, this Court should vacate the invalidation of the IBS-D Claims and remand to the district court.

With respect to the Polymorph Claims, skilled artisans did not reasonably expect that rifaximin was polymorphic, much less know that a form with the specific claimed x-ray diffraction peaks existed. Because, as in *Pharmacyclics*, there was neither a motivation nor an expectation of success in creating the claimed rifaximin polymorph β, this Court should reverse the judgement that the Polymorph Claims are invalid, render judgment that Norwich failed to show invalidity, and order the FDA not to approve Norwich's ANDA until at least the expiration of the Polymorph Patents.

Dated: July 24, 2023

Respectfully submitted,

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# ADDENDUM

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IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

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|---|---|
| SALIX PHARMACEUTICALS, LTD.; SALIX PHARMACEUTICALS, INC.; BAUSCH HEALTH IRELAND LTD.; ALFASIGMA S.P.A.,<br><br>Plaintiffs,<br><br>v.<br><br>NORWICH PHARMACEUTICALS, INC.,<br><br>Defendant. | Civil Action No. 20-430-RGA |

TRIAL OPINION

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August 10, 2022

**ANDREWS, U.S. DISTRICT JUDGE:**

Salix sued Norwich for infringement of twenty-six patents that cover Salix's branded Xifaxan (rifaximin) 550 mg tablets. (D.I. 59 ¶¶ 12, 41). Before trial, Salix narrowed its case to U.S. Patent Nos. 7,612,199, 7,902,206 ("the Polymorph Patents"), 8,642,573, 9,421,195, 10,335,397 ("the HE Patents"), 8,309,569, and 10,765,667 ("the IBS-D Patents"). In March 2022, I held a four-day bench trial. (D.I. 168–172, hereinafter "Tr.").

## I. BACKGROUND

Norwich submitted an Abbreviated New Drug Application (ANDA) to the Food and Drug Administration (FDA) for approval to market a generic version of Xifaxan. Salix alleges infringement under § 271(e)(2)(A) of the Patent Act. 35 U.S.C. §271(e)(2)(A). Norwich counters that the asserted patents are invalid.

In 2004, the FDA approved Xifaxan (rifaximin) 200 mg tablets to treat travelers' diarrhea. (D.I. 155 ¶ 9). On March 24, 2010, the FDA approved Xifaxan (rifaximin) 550 mg tablets to reduce the risk of overt hepatic encephalopathy ("HE") recurrence in adults. (*Id.* ¶10). On May 27, 2015, the 550 mg tablets were approved to treat irritable bowel syndrome with diarrhea ("IBS-D") in adults. (*Id.* ¶11). The asserted patents cover a polymorphic form of rifaximin and methods of treating HE and IBS-D in adults.

## II. LEGAL STANDARD

### A. Infringement

A patent is directly infringed when a person "without authority makes, uses, offers to sell, or sells any patented invention, within the United States . . . during the term of the patent . . . ." 35 U.S.C. § 271(a). A two-step analysis is employed in making an infringement determination. *See Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 976 (Fed. Cir. 1995) (en banc), *aff'd*,

517 U.S. 370 (1996). First, the court must construe the asserted claims to ascertain their meaning and scope. *See id.* The trier of fact must then compare the properly construed claims with the accused infringing product. *See id.* This second step is a question of fact. *See Bai v. L & L Wings, Inc.*, 160 F.3d 1350, 1353 (Fed. Cir. 1998).

"Under § 271(b), whoever actively induces infringement of a patent shall be liable as an infringer." *Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1363 (Fed. Cir. 2003). To prevail on a theory of induced infringement, a plaintiff must prove (1) direct infringement and (2) "that the defendant possessed specific intent to encourage another's infringement and not merely that the defendant had knowledge of the acts alleged to constitute infringement." *Vanda Pharm. Inc. v. West-Ward Pharm. Int'l Ltd.*, 887 F.3d 1117, 1129 (Fed. Cir. 2019) (quoting *DSU Med. Corp. v. JMA Co.*, 471 F.3d 1293, 1306 (Fed. Cir. 2006)).

In a Hatch-Waxman case, a plaintiff "can satisfy its burden to prove the predicate direct infringement by showing that if the proposed ANDA product were marketed, it would infringe the [asserted patent]." *Vanda*, 887 F.3d at 1130. For method-of-treatment patents, if an ANDA applicant's "proposed label instructs users to perform the patented method . . . , the proposed label may provide evidence of [the ANDA applicant's] affirmative intent to induce infringement." *AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1060 (Fed. Cir. 2010). "When proof of specific intent depends on the label accompanying the marketing of a drug inducing infringement by physicians, the label must encourage, recommend, or promote infringement." *Vanda*, 887 F.3d at 1129 (cleaned up).

**B. Obviousness**

A patent is invalid as obvious under 35 U.S.C. § 103 if "the claimed invention as a whole would have been obvious to a person of ordinary skill in the art at the time the invention was

made." *Kahn v. Gen. Motors Corp.*, 135 F.3d 1472, 1479 (Fed. Cir. 1998). "Obviousness is a question of law based on underlying factual findings: (1) the scope and content of the prior art; (2) the differences between the claims and the prior art; (3) the level of ordinary skill in the art; and (4) objective considerations of nonobviousness." *In re Morsa*, 713 F.3d 104, 109 (Fed. Cir. 2013) (citations omitted).

To show a patent is obvious, a party "must demonstrate by clear and convincing evidence that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so." *InTouch Techs., Inc. v. VGO Commc'ns, Inc.*, 751 F.3d 1327, 1347 (Fed. Cir. 2014) (cleaned up). The overall inquiry into obviousness, though, must be "expansive and flexible." *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 415 (2007). In conducting the obviousness analysis, "a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *Id.* at 418.

**C. Written Description**

The written description "must clearly allow persons of ordinary skill in the art to recognize that the inventor invented what is claimed." *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed.Cir.2010) (en banc) (cleaned up). The test is whether the disclosure "conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Id.* This requires an "objective inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art." *Id.*

**D. Indefiniteness**

35 U.S.C. § 112 requires that claims "particularly point[] out and distinctly claim[] the subject matter." The claims, viewed in light of the specification and prosecution history, must

"inform those skilled in the art about the scope of the invention with reasonable certainty." *Nautilus, Inc. v. Biosig Instruments*, Inc., 572 U.S. 898, 910 (2014). "While a claim employing a term of degree may be definite where it provides enough certainty to one of skill in the art when read in the context of the invention, a term of degree that is purely subjective and depends on the unpredictable vagaries of any one person's opinion is indefinite." *Intell. Ventures I LLC v. T-Mobile USA, Inc.*, 902 F.3d 1372, 1381 (Fed. Cir. 2018) (cleaned up).

## III. THE POLYMORPH PATENTS

The Polymorph Patents claim polymorphic forms of rifaximin. Plaintiffs assert two such claims. Asserted Claim 4 of the '199 patent states:

> 4. Rifaximin in polymorphic form β, wherein the rifaximin has x-ray powder diffraction pattern peaks at about 5.4°; 9.0°; and 20.9° 2θ and wherein the rifaximin has a water content of greater than 5%.

Asserted Claim 36 of the '206 patent depends on claim 34:

> 34. A solid pharmaceutical composition comprising rifaximin in polymorphic Form β and a pharmaceutically acceptable excipient or carrier, wherein the rifaximin Form β has x-ray powder diffraction pattern peaks at about 5.4°; 9.0°; and 20.9° 2-θ.
>
> 36. The pharmaceutical composition of claim 34, wherein the rifaximin Form β has a water content of between about 4.5% to about 40%.

### A. Findings of Fact

1. If approved, Norwich's ANDA product will infringe the asserted claims of the Polymorph Patents.
2. The priority date of the asserted polymorph claims is November 7, 2003.
3. A person of skill in the art (a "POSA") would have had a B.S. in chemistry, chemical engineering, or a related discipline with at least 3 years' experience in the pharmaceutical industry related to API manufacturing, crystallization, characterization, or evaluation of solid state forms. Or a POSA would have had an advanced degree with less or no experience.

4. The '199 patent is a continuation of, and contains substantially the same disclosures as, the '206 patent.
5. Rifaximin exists in polymorphic forms. Norwich's ANDA product comprises polymorphic form β.
6. X-ray powder diffraction (XRPD) peaks are an inherent characteristic of a polymorph. Each peak in an XRPD diffractogram is a structural element of that form. XRPD was routine as of the priority date.
7. A crystalline form of a known compound can be characterized by a subset of XRPD peaks. The subset of XRPD peaks at about 5.4°, 9.0°, and 20.9° 2θ was sufficient as of the priority date to distinguish rifaximin β from the other known rifaximin polymorphs.
8. Water content is an inherent characteristic of a crystal form that can be determined by routine testing methods such as Karl Fischer (KF) or thermogravimetric analysis (TGA).
9. Cannata, Marchi, and the Normix Label are prior art.
10. Cannata disclosed crystalline rifaximin, methods of making it, and that it had antibacterial properties.
11. The four post-filing references relied upon by Defendant's expert, Dr. Zaworotko, do not show that any of the Cannata methods produces rifaximin β every time.
12. Cannata does not inherently anticipate the asserted polymorph claims.
13. Marchi disclosed methods of preparing crystalline rifaximin, rifaximin's antibacterial properties, and that it could be used in pharmaceutical compositions with conventional pharmaceutically acceptable excipients or carriers.
14. The Normix Label describes the use of rifaximin as a pharmaceutical.

15. Cannata in view of common knowledge discloses each and every limitation of claim 4 of the '199 patent.

16. A POSA would have had a motivation to combine Cannata with commonly known testing techniques XRPD and KF or TGA because regulatory bodies instructed applicants to characterize the solubility, stability, and bioavailability of drug candidates.

17. A POSA would have had a reasonable expectation of success at characterizing the rifaximin β polymorph and arriving at the claimed XRPD peaks at about 5.4°, 9.0°, and 20.9° 2θ and water content of greater than 5%.

18. Marchi in view of Cannata and common knowledge discloses each and every limitation of claim 36 of the '206 patent.

19. A POSA would have had a motivation to combine Cannata with Marchi in light of common knowledge.

20. A POSA would have had a reasonable expectation of success at achieving a pharmaceutical composition comprising rifaximin β and a pharmaceutically acceptable excipient or carrier.

21. All rifaximin β claim limitations are expressly disclosed in the specifications of the Polymorph Patents..

**B. Infringement**

Norwich admits that its ANDA Product, if approved, will infringe claim 4 of the '199 patent and claim 36 of the '206 patent. (D.I. 148, Ex. 1, ¶¶ 126, 127).

### C. Invalidity

#### 1. Inherent Anticipation

Each expert asserts that his validity analysis is not impacted by which definition of a POSA I use. (Tr. 860:7-861:8; Tr. 936:21-937:13). In view of Defendant's burden to prove invalidity by clear and convincing evidence, I will adopt Plaintiffs' definition of a POSA.

Norwich argues that U.S. Patent No. 4,557,866 (the "Cannata" reference) (JTX-37) inherently anticipates claim 4 of the '199 patent because it discloses a process that necessarily produces the claimed rifaximin β. (D.I. 176 at 32). "[A] prior art reference may anticipate without disclosing a feature of the claimed invention if that missing characteristic is necessarily present, or inherent, in the single anticipating reference." *Schering Corp. v. Geneva Pharms., Inc.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003). A disclosed process may anticipate "if it discloses in an enabling manner the production" of the claimed polymorph. *SmithKline Beecham Corp. v. Apotex Corp.*, 403 F.3d 1331, 1344 (Fed. Cir. 2005).

Here, the issue is whether the process disclosed by Cannata invariably produces rifaximin β. Norwich has presented the following evidence in support:

- The "Viscomi Declaration," a declaration to the PTO stating that samples of batches produced according to Cannata "are composed either of mixture of polymorph (alpha and beta, and in some case alpha and epsilon) or different polymorphs." (JTX 80 ¶ 7).
- The "Viscomi 2008" article, which Norwich's expert Dr. Zaworotko testified shows that rifaximin β is a necessary precursor to the formation of rifaximin α, δ, and ε. (JTX 65; Tr. 880:20-881:1, 921:24-922:6).
- The "Braga 2012" article, which describes the inherent properties of rifaximin β. (JTX 105).
- The "Bacchi 2008" article, which described rifaximin beta 4 ("RX4"), a substance the author concluded was "the so-called beta rifaximin of the literature." (DTX 43; Tr. 882:14–24). The article describes slow evaporation as the method of preparation. From this article, Dr. Zaworotko concluded, "Examples 1 and 7, at the very least, of Cannata would have . . . necessarily afforded rifaximin Beta because of the solvent system used, the method used of controlled crystallization, and the lack of drying or lack of aggressive drying." (Tr. 883:6–10).

According to this evidence, Norwich argues, "Cannata inherently produced rifaximin β every time, either directly *or as a necessary precursor* to the α, δ, and ε forms and mixtures disclosed in the Viscomi Declaration." (D.I. 185 at 9).

I do not think this evidence amounts to clear and convincing evidence that Claim 4 is inherently anticipated by Cannata. Norwich could have shown anticipation either because (1) as a law of nature, rifaximin α, δ, and ε cannot exist without having been derived from rifaximin β, or (2) a method disclosed in Cannata produces rifaximin β each and every time it is practiced. Dr. Zaworotko's testimony did not prove either.

Dr. Zaworotko's opinion does not clearly support the conclusion that, as a law of nature, rifaximin β is a necessary precursor to rifaximin α, δ, and ε. For one thing, had that been his opinion, he could have clearly stated that, and I do not think he did. (*See* Tr. at 870-884). I think Dr. Zaworotko's opinion was relying upon the Viscomi 2008 article:

> Q: Would rifaximin Beta form as a precursor to any polymorph listed in the Viscomi declaration listed at paragraph 7?
>
> A: Yes, based upon the Viscomi 2008 article, where the effect of moisture on rifaximin crystal forms was studied and based upon the diagram [derived from Viscomi 2008] it's clear that Beta has to be the precursor for any of the other crystal forms with lower water content.

(Tr. 921:25–922:1). This opinion appears to be based on Dr. Zaworotko's reading of Viscomi 2008, and not a conclusion that rifaximin α, δ, and ε cannot exist in the world without having first been rifaximin β. I think Dr. Zaworotko stated his opinion the way he did because the "diagram" to which Dr. Zawortko refers, which is based on Figure 4 ("The relationship between the various crystal forms of rifaximin"), was not the main point of the article. The article's purpose, consistent with its title ("Crystal forms of rifaximin and their effect on pharmaceutical properties") was to report on a "study [] to identify the presence of crystal forms of rifaximin

and to assess their impact on parameters such as solubility, intrinsic dissolution and bioavailability." (JTX-65 at 1074). The paper concluded, "The unexpected outcome of this study is that we have found that some crystal forms of rifaximin are significantly absorbed, while it was previously considered a non-absorbable drug. These finding[s] indicate the need of putting appropriate manufacturing and analytical procedures in place to consistently yield rifaximin of the appropriate crystalline structure." (*Id.* at 1080). Thus, to the extent Dr. Zaworotko was offering an opinion that Viscomi 2008 is conclusive proof that rifaximin α, δ, and ε are necessarily derived from rifaximin β, I do not find that conclusion to be well-supported. It is not clear and convincing proof.

Thus, to show that Cannata inherently anticipates Claim 4, Norwich would need to show that every time Cannata is performed, rifaximin β is produced. Norwich has not done so.

The Viscomi Declaration does not help Norwich. It stated that among "samples of batches" produced according to Cannata, when retested in 2006, there were four batches with no rifaximin β. The four batches consisted of (1) only the "delta polymorph," (2) only of the "epsilon form," (3) a mixture of "the alpha and epsilon form," and (4) a mixture of the "alpha and delta forms," respectively. (JTX-80, ¶7; *see* Tr. 949:8-12).

Although Viscomi 2008 states that the "method of production of rifaximin" was disclosed in European Patent No. 161534, the counterpart to Cannata, Salix has persuasively argued that Viscomi 2008 discloses steps that are more specific than what Cannata describes. (*See* JTX 105 at 6404 n.3; JTX 65 at 1074 & 1074 n.29; Tr. 874:16-25).

In Viscomi 2008, the reaction step for preparing wet rifaximin describes (1) heating the reaction mixture to 50°C for 5 hours, then cooling it to 20°C; (2) adding a mixture of 0.1 moles of ascorbic acid and 2.5 moles of concentrated hydrochloric acid in 220 mL of 58% ethyl alcohol

in water over 30 minutes; and (3) adding concentrated hydrochloric acid dropwise until pH 2.0 is reached. (Tr. 951:8-13; JTX 65 at 1074). Cannata has none of these details. (Tr. 951:13-17). The crystallization step in Viscomi is also described with more precision than in Cannata. (Tr. 951:18–952:2).

Similarly, Bacchi 2008 discloses a process that does not precisely match Cannata's examples 1 and 7. Bacchi describes using a "slow evaporation" process while Cannata does not mention evaporation. (DTX 43 at 1734; Tr. 949:20-22). Furthermore, the Cannata examples crystallize rifaximin from a 7:3 ethanol to water mixture, whereas Bacchi does not disclose any ethanol to water ratio. (Tr. 949:15-23; Tr. 953:2-954:3).

Ultimately, it appears that Cannata left certain steps up to the discretion of the chemist preparing the rifaximin. To show that Cannata invariably produces rifaximin β, Norwich would have needed to show that, no matter how the chemist exercised his or her discretion, rifaximin β would be produced. I do not think Norwich has done so. "Experiments that do not follow the prior art procedure alleged to inherently anticipate cannot show inherent anticipation." *Merck & Cie v. Watson Lab'ys, Inc.*, 125 F. Supp. 3d 503, 513 (D. Del. 2015) (cleaned up), *rev'd on other grounds*, 822 F.3d 1347 (Fed. Cir. 2016).

Thus, I find that Norwich has not shown by clear and convincing evidence that claim 4 of the '199 patent is inherently anticipated by Cannata.

**2. Obviousness**

Norwich contends that claim 4 of the '199 patent is obvious over Cannata in view of common knowledge. (D.I. 176 at 34–35). Norwich contends that claim 36 of the '206 patent is obvious over Cannata in view of the Normix Label and common knowledge or over Marchi in view of Cannata and common knowledge. (*Id.* at 35).

A POSA would have understood from Cannata that rifaximin exists in crystalline form and that rifaximin has "outstanding antibacterial properties." (JTX 37 at 3:10–16, 5:21–36). Norwich argues this knowledge would motivate a POSA to "identify the characteristics of the obtained rifaximin" using "routine methods." (D.I. 176 at 35). Furthermore, Norwich argues that a POSA would recognize "that the crystallization solvent used by Cannata included water, which could lead to hydrate formation, and thus [the POSA] would have been motivated to analyze the effect of water on the crystalline form using conventional methods." (*Id.*). A POSA could have performed a "routine humidity experiment . . . in one day and detected rifaximin β." (*Id.*).

The Court of Appeals considered the obviousness of a polymorph patent in *Grunenthal GmbH v. Alkem Labs. Ltd.*, 919 F.3d 1333, 1336 (Fed. Cir. 2019). The *Grunenthal* patent claimed Form A of tapentadol hydrochloride characterized by its XRPD peaks. *Id.* The *Grunenthal* defendant, Alkem, argued that the claim was obvious in light of prior art that disclosed a Form B of tapentadol hydrochloride. *Id.* at 1337.

Alkem's prior art references included (1) the prior art patent that described a crystalline form of tapentadol hydrochloride (later called "Form B") and (2) an article that "outlines a number of variables that may be adjusted during the recrystallization process to determine whether polymorphism occurs in a compound." *Id.* at 1337, 1341. The "polymorphism of tapentadol hydrochloride was unknown at the time of filing the [asserted patent]," and "Form B was the only crystal structure . . . known in the art at the time." *Id.* at 1341.

The Court of Appeals found that the article did not provide "guidelines regarding which [variables] are likely to result in polymorphs of particular compounds." *Id.* at 1342. Thus, the article did little more than tell a POSA to "vary all parameters or try each of numerous possible

choices until one possibly arrived at a successful result," which does not provide a reasonable expectation of success. *Id.* (quoting *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1365 (Fed. Cir. 2007)).

Here, the prior art includes Cannata, which discloses processes for preparing a crystalline form of rifaximin. As in *Grunenthal*, rifaximin's polymorphism was unknown as of the priority date. In *Grunenthal*, however, the prior art patent was known to produce a particular form—Form B—of tapentadol hydrochloride. Here, by contrast, no rifaximin had been publicly characterized as a particular form as of the priority date.

I think the evidence is clear and convincing that a POSA would have been motivated to characterize the rifaximin produced by the Cannata processes. Cannata disclosed that rifaximin had strong antibacterial properties and low bioavailability, motivating a POSA to evaluate the substance as a potential drug candidate. (JTX 37 at 3:10-16; JTX 94 at 6-7; Tr. 869:16–870:4; Tr. 891:16-892:12). The FDA encouraged, if not required, that the solid forms of a drug substance be well-characterized during drug development, including as to the properties of solubility, stability, and bioavailability. (DTX 315-35; Tr. 892:13-894:7). XRPD profiling was the predominant method for identifying crystalline materials. (DTX 315-38; Tr. 894:23-895:12). FDA guidance required "appropriate manufacturing and control procedures" when manufacturing and storing the drug substance could result in a hydrated drug substance. (DTX 315-39; Tr. 895:13–24). Because the Cannata process for preparing rifaximin used water, a POSA would know about the potential for a hydrate to form, and be motivated to perform routine testing (e.g., KF or TGA) for water content and hydration formation. (DTX 317-19; JTX 54 at 182; Tr. 888:3-890:5; DTX 315-39).

I think the evidence shows that a POSA would have a reasonable expectation of success in characterizing the polymorph β, as opposed to the other forms of rifaximin. Although Norwich's evidence failed to show that β was produced each and every time rifaximin was prepared according to Cannata, it did strongly suggest that polymorph β is a commonly produced polymorph and the most stable form of rifaximin.

The Viscomi Declaration stated that rifaximin prepared according to Cannata yielded β along with other polymorphs. (JTX 80 at ¶ 7). Dr. Zaworotko explained that β is the most stable form. Tr. 877:17–18. ("[B]eta is the winner in terms of stability under normal conditions of temperature and humidity."). Dr. Myerson's critiques of Dr. Zaworotko's testimony do not have the same force in the context of obviousness as they did in the context of inherent anticipation. While Viscomi 2008's increased specificity in the method of preparation suffices to suggest that Cannata may not produce rifaximin β each and every time (as would be required for inherent anticipation), the standard for obviousness is a reasonable expectation of success. *See Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006) ("While the definition of 'reasonable expectation' is somewhat vague, our case law makes clear that it does not require a certainty of success.").

I reject Salix's argument that a POSA would not have been able to predict the precise peaks that characterize rifaximin β, and accordingly a POSA would not have had a reasonable expectation of success. The Federal Circuit has held, "[A] rule of law equating unpredictability to patentability, applied in this case, would mean that any new salt . . . would be separately patentable, simply because the formation and properties of each salt must be verified through testing. This cannot be the proper standard since the expectation of success need only be reasonable, not absolute." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007). I

think the same is true in this context. I credit the testimony of Dr. Zaworotko that the XRPD peaks and water content are "inherent" properties of a crystal form that can be tested using routine methods. (Tr. 871:20–872:5; 884:2–13; 895:8–12). Thus, a POSA would have a reasonable expectation of success at characterizing the polymorph and arriving at the claimed XRPD peaks and water contents.[1]

There is no evidence of secondary considerations of nonobviousness for the Polymorph Patents. (*See* D.I. 174 at 15–18).

Thus, I find by clear and convincing evidence that claim 4 of the '199 patent is obvious in light of Cannata in view of common knowledge.

Claim 36 of the '206 patent claims a pharmaceutical composition comprising (1) rifaximin β with the claimed XRPD peaks and a water content between about 4.5% to 40% and (2) a pharmaceutically acceptable excipient or carrier.

Norwich argues that rifaximin had previously been formulated as a pharmaceutical composition comprising pharmaceutically acceptable excipients or carriers. (D.I. 176 at 37). Marchi in 1982 and the Normix Label in 2001 each taught "pharmaceutical compositions" comprising rifaximin. (*Id.*). Marchi disclosed that rifaximin can be used as an "antibacterial agent[]" in pharmaceutical compositions with conventional pharmaceutically acceptable excipients or carriers. (JTX 48 at 4:27-33, 4:67-5:4, 5:14-40, 60-62, 6:6-31, Cls. 10–11; Tr. 865:10-866:12, 868:20-869:3). The Normix Label disclosed that rifaximin was an approved antibacterial drug in Italy in 1985 as a coated tablet comprising 200 mg of rifaximin and

[1] Plaintiffs call to my attention *Pharmacyclics LLC v. Alvogen Pine Brook LLC*, 556 F. Supp. 3d 377, 412 (D. Del. 2021), *app. filed*, No. 21-2270 (Fed. Cir. Aug. 31, 2021). (D.I. 181 at 37). I have considered that case but I do not agree with it on this point.

pharmaceutically acceptable excipients. (JTX 94 at 5, 7-8; Tr. 867:13-17, 869:10-870:4, 903:3-9).

Norwich further argues that rifaximin's antibacterial properties were known. Cannata taught that rifaximin has outstanding antibiotic properties and has poor absorption, which indicates to a POSA that it could be used for GI treatments. (Tr. 862:22–24; 863:14–18). Marchi also disclosed "remarkable" antibacterial properties. (JTX 48 at 4:27-33, 4:67-5:4, 5:14-40, 5:60-62, 6:6-31, Cls. 10–11; Tr. 865:10-866:12, 868:20-869:3).

Salix did not respond to these arguments. (*See* D.I. 181 at 37–39).

The only difference between the previous pharmaceutical compositions of rifaximin and claim 36 is that claim 36 characterizes rifaximin as polymorphic form β. Rifaximin β is obvious over Cannata in view of common knowledge, for the same reasons as previously stated in connection with asserted claim 4 of the '199 patent. Accordingly, I find that a POSA would have had the motivation to combine the prior art references of Cannata, the Normix Label, or Marchi and Cannata, in view of the commonly known testing techniques, with a reasonable expectation of success in doing so. Salix offers no evidence or arguments to the contrary. Thus, Norwich has proved by clear and convincing evidence that claim 36 of the '206 patent is invalid as obvious.

**3. Written Description**

The asserted claims describe rifaximin β as having XRPD peaks "at about 5.4°, 9.0°, and 20.9° 2θ." '199 Patent, Cl. 4, '206 Patent, Cl. 36. The specification states that rifaximin β is "characterized . . . by a powder X-ray diffractogram (reported in FIG. 2) which shows peaks at the values of the diffraction angles 2θ of 5.4°; 6.4°; 7.0°; 7.8°; 9.0°; 10.4°; 13.1°; 14.4°; 17.1°;

17.90°; 18.30°; 20.9°." '199 Patent 5:64–6:3. Norwich argues that the polymorph patents improperly claim a genus, whereas the specification recites only a species. (D.I. 176 at 37–38).

Salix responds that (1) the claims, on their face, are limited to the specific polymorphic form rifaximin β, rendering Norwich's genus characterization inaccurate, and (2) even if Norwich is right, the claims identify structural features common to the genus as required by the caselaw. (D.I. 181 at 39–42). I agree with Salix on the first point, and accordingly will not address Salix's second argument.

The evidence shows that a subset of XRPD peaks can identify the polymorph. The "normal practice at the USPTO" is to claim a polymorphic form using "at least three powder diffraction pattern peaks." (Tr. 965:11–17; JTX 28 at XIFAX_NOR_0002208). Dr. Zaworotko's own patent explains, "For XRPD data herein, each composition of the present invention[, a new crystalline form of a known compound,] may be characterized by any one, any two, any three, any four, any five, any six, any seven, or any eight or more the 2θ angle peaks." (Tr. 916:17–917:18, PTX 707 at 15:36–39). I do not think the asserted claims claim a genus. They claim only rifaximin β, a polymorphic form which can be identified using the three peaks recited in the claims.

Thus, I reject Norwich's written description challenge.

## IV. THE METHOD PATENTS

### A. Inducement

#### 1. Findings of Fact

1. At least some physicians will review Norwich's label.
2. Physicians will instruct patients to take rifaximin according to the instructions on the label.

**2. Infringement**

Before turning to a limitation-by-limitation infringement analysis for the method patents, I will address an underlying dispute regarding induced infringement when the patient is the one performing the patented method. Inducement requires direct infringement. Salix argues that either (1) the patients, in taking rifaximin, will directly infringe "because patients will read and follow the instructions in Norwich's Label (with or without the help of their physician)," or (2) physicians and patients will jointly infringe based on the label. (D.I. 174 at 4). I do not think there is joint infringement. I find that Plaintiffs have not shown that doctors condition the patient's receipt of a rifaximin prescription on the performance of particular steps in the way contemplated by *Akamai*. *See Akamai Techs., Inc. v. Limelight Networks, Inc.*, 797 F.3d 1020, 1023 (Fed. Cir. 2015) (en banc). Rather, the patients directly infringe.

According to Norwich, "Because patients will not take rifaximin correctly without physician instruction, the Norwich Label does not induce patients and cannot be the basis for finding specific intent." (D.I. 183 at 3–4 (citation omitted)). Essentially, because there is another party involved in the inducement (physicians), the "chain of events leading to infringement is . . . too attenuated to prove specific intent." (D.I. 183 at 6–7). I disagree. The Court of Appeals has long held, "the sale of a product specifically labeled for use in a patented method constitutes inducement to infringe that patent[.]" *Eli Lilly & Co. v. Actavis Elizabeth LLC*, 435 F. App'x 917, 926 (Fed. Cir. 2011). In the context of a prescription medication, physicians have a particularly important role in conveying essential information to patients. The evidence in this case bears this out. (*See* Tr. 66:22-69:20; Tr. 119:5-120:16 (describing the process of prescribing rifaximin to patients)). Other areas of law, such as the learned intermediary doctrine, recognize the physician's essential role in communicating information about a medication to the patient. *See Reyes v. Wyeth*

*Lab'ys*, 498 F. 2d 1264, 1276 (5th Cir. 1974). A pharmaceutical company, such as Norwich, is well aware of how doctors prescribe medications to patients. Thus, if there will be direct infringement, then Norwich will have the specific intent to induce patients' direct infringement.

**B. The HE Patents**

HE is a liver disease that affects the brain. (Tr. 41:15-21; 48:10-16). For patients with HE, the liver does not properly filter toxins from the blood. These toxins can cause changes to the patient's mental state. (*Id.*) Physicians grade HE severity using the Conn score, which ranges from 0 to 4. (Tr. 45:14–47:4). Conn scores of 0 or 1 reflect a normal or near-normal mental state. A Conn score of 2 or higher reflects more serious symptoms, from obvious personality changes to stupor or even coma. (Tr. 46:6–11, 14–15). Conn scores of 0 and 1 cannot be detected in a routine physical exam. (Tr. 45:20–21; 46:4–5). Physicians also assess HE severity using an asterixis score. (Tr. 346:5–8). Asterixis occurs when a patient cycles between lower and higher levels of consciousness and can be measured by tremors in a patient's outstretched hand. (Tr. 46:16–47:4).

HE can be either episodic or persistent. (Tr. 44:13–25). Persistent HE is characterized by a Conn score that remains at 2 or above. (Tr. 44:24–25). Patients with episodic HE have periods of remission punctuated by episodes of breakthrough overt HE. (Tr. 44:13–25; 45:14–46:15). An episode of "breakthrough overt HE" is an increase in the patient's Conn score to grade 2 or higher (e.g., going from 0 or 1 to 2 or more), or an increase in the patient's Conn and asterixis scores of one grade each with a baseline Conn Score of 0. (D.I. 149, Ex. 1 ¶ 81). Patients with a history of overt HE who are not currently having an overt HE episode are in "remission of HE." (*Id.* ¶ 81; Tr. 48:2–6). Thus, patients with a Conn score of 0 or 1 and no asterixis are in remission. (Tr. 48:2–6). After a first overt HE episode, only about half of patients will live one year. (Tr. 50:6–19).

Plaintiff asserts four method claims in connection with the HE patents.

Asserted Claim 6 of the '195 patent is a dependent claim with three elements: (1) reducing the risk of HE recurrence, (2) by orally administering about 550 mg of rifaximin twice daily (BID) to the adult subject, (3) for a period of 12 months or longer.

Asserted Claim 8 of the '573 patent is a dependent claim with three elements: (1) maintaining remission of HE, wherein remission is defined as a Conn score of 0 or 1, (2) by administering 550 mg of rifaximin to the subject BID, (3) for a period of 12 months or longer.

Asserted Claim 11 of the '397 patent is a dependent claim with four elements: (1) reducing a subject's risk of experiencing a breakthrough overt HE episode, (2) by orally administering to the subject 550 mg of rifaximin BID, (3) for a period of about 12 months or longer, (4) to a subject with a Conn score of 0 or 1.

Asserted Claim 12 of the '397 patent is a dependent claim with five elements: (1) reducing a subject's risk of experiencing a breakthrough overt HE episode, (2) by orally administering to the subject between about 1000 mg to about 1200 mg of rifaximin daily, (3) for a period of about 12 months or longer, (4) to a subject with a Conn score of 0 or 1, (5) "further comprising administering lactulose."

**1. Findings of Fact**

1. Norwich has knowledge of the HE patents.
2. Norwich's label will encourage administration of rifaximin for 12 months or longer.
3. Norwich's label will encourage administration of rifaximin for the "reduction in risk of overt hepatic encephalopathy (HE) recurrence in adults."
4. Norwich's label will encourage administration in patients having a Conn score of 0 or 1.

5. Norwich's label will encourage at least some physicians to co-administer rifaximin and lactulose.
6. Patients will take rifaximin according to the instructions on the label and will directly infringe the asserted HE claims.
7. Norwich's label will induce infringement of the asserted HE claims.
8. The priority date of the asserted claims is October 2, 2008.
9. A POSA would have had a Ph.D. in pharmacology, biology, biomedical sciences, microbiology and/or an M.D. with board certification in gastroenterology. He or she would have had training in or experience with liver and GI disorder research. If needed, a POSA would have collaborated with others having ordinary skill in areas relevant to the claimed subject matter, including infectious diseases and microbiology.
10. The Salix Presentation was not publicly accessible as of the priority date and is not prior art.
11. Leevy 2007 does not disclose a method of administering rifaximin to maintain remission.
12. As of the priority date, a 12-month duration for the administration of rifaximin was not within the common knowledge of a POSA.
13. The claimed method met a long-felt need of reducing the risk of HE recurrence and maintaining remission.
14. There was skepticism in the industry regarding the long-term use of antibiotics to maintain remission in HE patients.
15. The HE patents are not invalid as obvious.
16. The specification describes using rifaximin with or without lactulose.
17. A POSA would recognize that the inventors had possession of the claimed method.

**2. Infringement**

**i. Administering for 12 Months or Longer (All Claims)**

It is more likely than not that Norwich's Label will encourage administration of the ANDA product for 12 months or longer in at least some patients, and that Norwich knows and specifically intends for this period of administration. Norwich's product is indicated for reducing overt HE recurrence. (JTX 73 § 1.2). HE is chronic. It must be managed until the patient gets a liver transplant or dies. I credit the testimony of Drs. Mahl and Brown that they have had HE patients maintain remission of HE for 12 months while on rifaximin 550 mg BID. (Tr. 120:21–24; Tr. 55:3–11). The label has no recommendation as to duration of administration. The label further describes a study in which some patients used the product for 12 months or longer. Taken together, this evidence demonstrates by a preponderance of the evidence that Norwich's label would encourage administering rifaximin for at least 12 months.

**ii. Maintaining Remission ('573 Patent, Claim 8)**

I find that Salix has proved by a preponderance of the evidence that Norwich's label instructs as to "maintaining remission of HE" as required by the asserted claims. Norwich's label is indicated for the "reduction in risk of overt hepatic encephalopathy (HE) recurrence in adults." (JTX 73 § 1.2). The experts described "reducing the risk of overt HE recurrence" and "maintaining remission of HE" as "basically synonymous" or a "continuum of the same thing." (Tr. 249:23–250:18, 252:9–18; Tr. 51:21–52:19). Remission is binary—either a patient is in remission or the patient is not. An overt HE recurrence ends remission. Thus, to maintain remission, a patient must avoid overt HE recurrence.

**iii. Conn Score of 0 or 1 ('397 Patent, Claims 11 and 12)**

Norwich's label will more likely than not induce use of rifaximin in patients with a Conn score of 0 or 1. The label encourages use to prevent an overt HE recurrence, which as I have found, means maintaining remission. The evidence shows that patients in remission of HE have a Conn score of 0 or 1. Thus, the label will encourage the use of rifaximin in patients who have a Conn score of 0 or 1. This conclusion is bolstered by the Clinical Studies section, which describes a clinical study in which the patients were "defined as being in remission (Conn score of 0 or 1) from hepatic encephalopathy." (JTX 73 § 14.2).

Norwich argues that (1) doctors do not calculate a Conn score for their patients before prescribing rifaximin, and (2) the Indications section does not reference the Clinical Studies section and thus it "merely describe[es] a parameter of the study, rather than actually encouraging, recommending, or promoting" the infringing use. (D.I. 183 at 10). I find these arguments unpersuasive.

The expert testimony shows that at least some physicians use Conn scores in clinical practice. (Tr. 154:2–22; 264:6–7). Defendant's expert, Dr. Mahl, testified that he does not calculate Conn scores but does record the "elements that might go into a Conn score." (Tr. 114:16–20). The patents do not require the calculation of a Conn score. Rather, they require use in patients with a Conn score of 0 or 1, which can be present regardless of whether it has been calculated. On this testimony, it seems likely that Norwich's ANDA product will be used in at least some patients who have a calculated Conn score of 0 or 1 as well as patients whose Conn scores would be a 0 or 1, if calculated, based on the symptoms observed by their physicians.

Regarding the Clinical Studies section, the law does not require the indication section of a label to specifically direct the reader to look at other sections in order for those other sections to

be considered. The Court of Appeals has held, "The jury was entitled to credit expert testimony regarding the label's instructions on who should take what drug, when, why, and how, and to reject the argument that certain portions of the label were disjointed from others." *GlaxoSmithKline LLC v. Teva Pharms. USA Inc.*, 7 F.4th 1320, 1329 (Fed. Cir. 2021), *petition for cert. filed*, No. 22-37 (July 11, 2022). I credit the testimony of Dr. Brown that physicians commonly read the Clinical Studies section. (Tr. 67:24–68:8). The "Hepatic Encephalopathy" subsection starts with the sentence: "The efficacy of rifaximin tablets 550 mg taken orally two times a day was evaluated in a randomized, placebo-controlled, double-blind, multi-center 6-month trial of adult subjects from the U.S., Canada, and Russia who were defined as being in remission (Conn score of 0 or 1) from hepatic encephalopathy (HE)." (JTX 73 § 14.2). Accordingly, I find that the label will induce use in patients with a Conn score of 0 or 1.

**iv. Administration with Lactulose ('397 Patent, Claim 12)**

Norwich's label will encourage co-administration with lactulose. In the Indications and the Clinical Studies section, the label notes that 91% of patients took rifaximin and lactulose concomitantly, and that lactulose did not alter the treatment effect of rifaximin. (JTX 73 §§ 1.2, 14.2). This strongly suggests that taking lactulose concomitantly is safe and effective, and it will likely encourage some physicians to administer rifaximin in conjunction with lactulose as required by the claims. I reject Norwich's comparison to *Shire LLC v. Amneal Pharmaceuticals*, which held that label indicating that a drug could be taken "with or without" food was "indifferent" as to which option was select and thus not an instruction to infringe. 2014 WL 2861430, at *5 (D.N.J. June 23, 2014), *aff'd in part, rev'd on other grounds*, 802 F.3d 1301 (Fed. Cir. 2015). The high percentage of patients who took lactulose concomitantly, and the fact that this information was included in the Indications section, encourages physicians to prescribe the two concomitantly.

I credit the testimony of Dr. Brown, who stated that the label, by citing the 91 percent figure, "makes clear that you can – you can and probably should use Lactulose in the majority of your subjects." (Tr. 76: 5–7). I further credit Dr. Brown's testimony, "Whenever possible, I use the combination of Lactulose and rifaximin because that's where the bulk of the data is." (Tr. at 76:12–13). I find that a physician reading the Norwich label and considering a study in which 91% of the patients were administered lactulose concomitantly will be inclined to do so likewise "because that's where the bulk of the data" showing the efficacy of rifaximin is.

**v. Substantial Noninfringing Use (All Claims)**

Norwich argues that its ANDA product has substantial noninfringing uses, which is relevant to intent to induce. (D.I. 183 at 11–12). Most HE patients live less than 12 months after their first overt HE episode. Thus, a substantial number of patients taking Norwich's ANDA as directed will not take rifaximin for 12 months or more, and these uses will not meet the 12-month-or-more claim limitation. Norwich points to *Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1363–66 (Fed. Cir. 2003) in support of this argument.

The Federal Circuit has distinguished *Warner-Lambert*, where the infringing use would be off-label use of the defendant's ANDA product and encompass only a small number of sales, and cases where "the proposed label itself recommends infringing acts." *Vanda Pharms. Inc. v. West-Ward Pharms. Int'l Ltd.*, 887 F.3d 1117, 1132–33 (Fed. Cir. 2018). Here, since I find that the label itself recommends infringement, the potential for substantial non-infringing uses does not negate Norwich's intent to induce infringement.

**3. Invalidity**

The parties agree that the definition of a POSA is not outcome determinative. (D.I. 176 at 2; D.I. 181 at 1). I adopt Plaintiffs' definition of a POSA.

Norwich argues that as of 2008, it was widely known that rifaximin was safe and effective for treating HE. (D.I. 176 at 3). Rifaximin was indicated abroad for HE in 2000. (JTX 94 at 5, 9). In 2004, the FDA approved Salix's Xifaxan for traveler's diarrhea. From that time, there is evidence of widespread off-label use of Xifaxan by physicians to treat patients with HE. Market research conducted by Salix shows that, by January 2007, 77% of physicians who treated HE patients had prescribed Xifaxan for HE. (DTX 349-16).

The prior art described the use of rifaximin in HE patients. For instance, a 1993 article ("Festi") described one open study and two randomized, controlled, comparative studies. The three studies "confirm[ed] the usefulness of rifaximin in the management of cirrhotic patients with mild HE." (JTX 42 at 607; Tr. 165:11-166:5). A 2000 article ("Williams 2000") described a study confirming that 1200 and 2400 mg doses of rifaximin showed significant improvement "in reducing objective parameters of HE in cirrhotic patients," and "treatment with rifaximin 1200 mg/day may be considered as an adjuvant or an alternative" to lactulose, with no adverse effects. (JTX 66 at 203-4, 207). Lactulose was the "mainstay" for HE therapy at the time. (*See* Tr. 203:17–204:5). In 2004, doctors at a Salix-hosted conference on hepatology reported being "very happy with [rifaximin's] results" and that rifaximin had "excellent" tolerability with "no significant side effects." (Tr. 172:10–18; 174:8-22; DTX 584-1, 3). A 2007 retrospective chart review ("Leevy 2007") showed better treatment outcomes for patients on rifaximin than on lactulose. (DTX 390-3; Tr. 204:6-16).

Norwich also points to retrospective chart reviews published after the priority date that show use of rifaximin for HE before the priority date. (*See* D.I. 176 at 9–10 (citing JTX 111, JTX 109)). I do not think these uses are in the prior art because there is no evidence that a POSA would have known about them. They do provide evidence of a POSA's state of mind, since the physicians

prescribing Xifaxan off-label meet both parties' definition of a POSA. (*See* D.I. 182 ¶ 121; D.I. 177 ¶ 1). *See In Re: Copaxone Consol. Cases*, 906 F.3d 1013, 1025 (Fed. Cir. 2018) (holding, "The district court . . . properly relied on [a reference] not as statutory prior art, but for the fact that [POSAs] were interested in pursuing less frequent dosing regimens.").

**i. Prior Art Combinations**

Norwich presents two obviousness combinations for the asserted HE claims: the Bausch HE Study in light of the Salix Presentation, and Leevy 2007 in light of common knowledge. I will consider each in turn.

The Bausch HE Study is the protocol for the clinical trial that ultimately led to the approval of rifaximin for HE. It disclosed the method, dosage, lactulose, and Conn score limitations of the asserted claims. The Salix Presentation was a presentation given by Dr. Leevy at a Salix shareholder's meeting in which Dr. Leevy described using rifaximin to treat HE. (DTX 52-4). Dr. Leevy described the duration limitation. Between the two, all claim limitations are disclosed.

Salix argues that the Salix Presentation was not in the prior art because it was not accessible. (D.I. 181 at 4). Salix tried to exclude the evidence before trial. (D.I. 150). I denied Salix's motion without prejudice to evaluating its prior art status based on a complete understanding of the record. (D.I. 161 at 28:9–18). Norwich's response to the motion in limine relied on evidence that Norwich did not present at trial. (*See* D.I. 150 at 9 of 18 (describing a Salix press release announcing the conference)). Accordingly, I will reconsider the question in light of the evidence presented at trial.

At trial, Defendant offered the transcript of the Salix Presentation and expert testimony regarding the presentation. (DTX 660; Tr. 175:20–176:22). Defendant's expert, Dr. Berg, testified that the Salix presentation was publicly available online at the SEC and that a POSA would be

motivated to find it because Salix was the only company selling rifaximin in the United States at the time. (Tr. 175:22–24; 176:15–22). Salix responds that this testimony is unsupported by explanation or evidence. (D.I. 181 at 4–5). While I credit Dr. Berg's assertions regarding a POSA's motivation to look for and methods of finding such a document, I do not credit his testimony regarding the availability of the Salix Presentation online before the priority date. I do not think a medical doctor's expertise is a basis for opining on what the SEC had available online more than a decade ago. Dr. Berg's opinion is not supported by independent evidence. "At this critical point in the determination of obviousness, there must be factual support for an expert's conclusory opinion." *Upjohn Co. v. Mova Pharm. Corp.*, 225 F.3d 1306, 1311 (Fed. Cir. 2000). Without evidence of online accessibility, and without evidence that the meeting was attended by interested POSAs (or even directed to POSAs, rather than investors), I find that Defendant has not shown by clear and convincing evidence that the Salix Presentation is prior art.

Norwich's second prior art combination is Leevy 2007 and common knowledge. Norwich argues, "Leevy 2007 disclosed the method, dosage, and Conn score limitations." (D.I. 176 at 8). Norwich argues that common knowledge supplies the missing limitations of duration (of 12 months or more) and lactulose. (*Id.* at 9).

Upon review of the evidence, I find that Leevy 2007 does not describe the method limitation. Independently, common knowledge cannot supply the duration limitation. I will address each in turn.

The claims are directed to maintaining remission or reducing the risk of breakthrough overt HE. Leevy 2007 concluded that HE hospitalizations were less frequent and shorter for patients on rifaximin than for patients on lactulose. Norwich argues that these hospitalizations are a metric for breakthrough overt HE and therefore Leevy 2007 discloses the method limitation. (D.I. 176 at

8). But Norwich's argument is not supported by the record. Norwich's expert, Dr. Berg, testified as to Leevy 2007's disclosure of rifaximin's ability "to treat HE" or as "therapy for HE." (*E.g.*, Tr. 181:9–18; 206:2–10). He did not characterize it as disclosing prevention or the like. I see no testimony linking Leevy's reduction in hospitalizations with the claimed method of preventing breakthrough overt HE.

Furthermore, Leevy 2007 did not track Conn scores throughout the study. As Salix argues, "a POSA would not have been able to determine whether subjects who had a Conn score of 1 at the beginning of the rifaximin phase maintained that Conn score throughout the 6 months." (D.I. 181 at 5). I credit Dr. Brown's testimony, "You cannot interpret the natural course of these patients' HE through the six-month period based on the data provided." (Tr. 393:4–6). Leevy 2007 does not teach the maintaining remission limitation.

Thus, Leevy 2007 cannot supply the limitations required for the asserted claims, whether it is maintaining remission of HE or reducing the risk for breakthrough overt HE. On that basis alone, Defendant fails to prove obviousness.

There is a second, independent basis to reject the prior art combination of Leevy 2007 and common knowledge. I do not think that a POSA would have a reasoned basis to resort to the "common sense" that rifaximin could be used for 12 months or longer. Common sense can supply a limitation missing from the prior art if a "searching" review of the prior art provides a "reasoned basis for resort to common sense." *Arendi S.A.R.L. v. Apple Inc.*, 832 F.3d 1355, 1363 (Fed. Cir. 2016).

Many of the sources Norwich relies upon to show long-term administration are not prior art. (*See* D.I. 176 at 9–10 (citing retrospectives published after the priority date and the Salix Presentation)). They were not, at that point, in the common knowledge of the field.

Administration of rifaximin for 12 months or more suggests prevention (i.e., maintaining remission or reducing the risk of overt HE recurrence), not mere treatment. Norwich argues, "[T]he record is replete with prior art disclosing the use of rifaximin in patients in remission from HE (i.e., having a Conn score of 0 or 1)." (D.I. 185 at 5–6). It is true that some of the studies included patients with Conn scores of 0 or 1. (JTX 66 at 205; JTX 42 at 607.) Many of these patients would have been in remission, but the sources discuss HE "treatment," not prevention or maintenance of remission. The Bausch HE study was the first prior art source to clearly articulate a desire to prevent hepatic encephalopathy. (DTX 52-4). As of the priority date, the Bausch Study did not have any results. Accordingly, I do not think that a 12-month treatment period was within the common knowledge as of the priority date.

Furthermore, Salix has presented evidence that a POSA would have known that long-term administration of rifaximin, an antibiotic, was risky. Not only could long-term use of antibiotics lead to a superinfection, which could kill the patient, but, "A POSA would have been concerned that if an HE patient developed clinical resistance to rifaximin, [the POSA] would not be able to administer rifaximin the next time the patient experienced an HE episode." (D.I. 181 at 11; Tr. 388:3–9). The parties' experts disagreed about the level of risk associated with long-term administration of rifaximin and how a POSA would consider that risk. I credit Dr. DuPont's testimony that without further studies, a POSA would have been reluctant to administer rifaximin long-term. (Tr. 467:7–12). Thus, I think that the prior art does not provide enough of a reasoned basis for supplying the duration limitation.

Finally, Salix has presented evidence of secondary considerations of nonobviousness that weigh in favor of finding the HE patents nonobvious. The claimed HE methods met a long-felt need for maintaining remission and reducing the risk of breakthrough overt HE episodes. Salix

argues, "As of October 2008, no drug had been approved for HE in over 30 years, and no drug had ever been approved to *prevent* HE recurrence." (D.I. 174 at 17). Norwich's expert responded that there was no need because physicians were already using a combination of rifaximin and lactulose to treat HE. (Tr. 222:7–20). As Salix points out, however, "Short-term, off-label use of rifaximin to *treat* HE did not meet a long-felt need for long-term *prevention* of HE recurrence." (D.I. 186 at 10).

There was also some skepticism in the industry. Salix points to comments from the FDA advisory committee expressing the concern "that indefinite use of rifaximin could change the gut flora and cause antibiotic resistance." (D.I. 174 at 17). Norwich argues that the FDA statements lack a nexus to the asserted claims. I disagree. "Where the offered secondary consideration actually results from something other than what is both claimed and novel in the claim, there is no nexus to the merits of the claimed invention." *Novartis AG v. Torrent Pharm. Ltd.*, 853 F.3d 1316, 1330 (Fed. Cir. 2017) (citation omitted). But here, the potential antibiotic resistance would have resulted from the claimed method of treatment. Accordingly, I give some weight to the FDA comments as evidence of skepticism.

Ultimately, I find that Norwich has not shown by clear and convincing evidence that the asserted HE claims are invalid as obvious.

**ii. Written Description**

Norwich argues, "Claim 8 of the '573 patent, claim 6 of the '195 patent, and claim 11 of the '397 patent are invalid for lack of written description because the specifications of the patents fail to show that the administration of rifaximin alone (*i.e.*, in the absence of concomitant administration of lactulose) achieves the claimed effects." (D.I. 181 at 16). Norwich's argument seems to be that the specifications lack data supporting the efficacy of rifaximin alone. (*See id.*).

This is not the standard for written description. The specifications all describe using rifaximin with or without lactulose. (JTX 19 at 16:62-17:3 ("This method includes: administering rifaximin to a subject daily that is being treated with lactulose, and tapering lactulose consumption…. In one embodiment, the baseline use of lactulose is no use."); JTX 11 at 16:62-17:3; JTX 22 at 10:49-57). I therefore find that Norwich has not shown a lack of adequate written description by clear and convincing evidence.

**C. THE IBS-D PATENTS**

Irritable bowel syndrome ("IBS") is characterized by symptoms including abdominal pain, bloating, frequency, urgency, gas, and changed bowel habits, such as diarrhea, constipation, or alternating diarrhea and constipation. (*E.g.*, Tr. 618:23–620:2). Subtypes of IBS include IBS with diarrhea (IBS-D), IBS with constipation (IBS-C), or IBS with alternating diarrhea and constipation (IBS-A). (Tr. 622:9–623:1). The IBS-D subtype comprises about one-third of IBS patients. (Tr. 622:21–623:1). IBS may be caused, for example, by abnormal motility, abnormal muscular coordination, changes in the microbiome in the colon or small intestine, intolerance to certain foods, or psychological factors. (Tr. 618:23–620:2).

Plaintiffs assert two claims in connection with the IBS-D patents.

Asserted Claim 3 of the '667 patent is a dependent claim that has three elements: (1) administering 550 mg of rifaximin three times a day (TID) for 14 days; (2) to treat one or more symptoms of IBS-D; (3) in a subject 65 years of age or older.

Asserted Claim 2 of the '569 patent is a dependent claim with two elements: (1) administering 550 mg of rifaximin TID for 14 days; and (2) after stopping rifaximin, achieving a durability of response that comprises about 12 weeks of adequate relief of symptoms.

### 1. Findings of Fact

1. Norwich is aware of the IBS-D patents.
2. Norwich's label will encourage administering rifaximin to adults aged 65 years or older with IBS-D.
3. Norwich's label will encourage administration of "one 550 mg tablet taken orally three times a day for 14 days" for the treatment of IBS-D, which inevitably will result in at least some patients having a durability of response comprising about 12 weeks of adequate relief after stopping rifaximin.
4. Patients will take rifaximin according to the label and will directly infringe the asserted IBS-D claims.
5. Norwich's label will induce infringement of the asserted IBS-D claims.
6. The priority date for the IBS-D claims is February 26, 2008.
7. A person of skill in the art would have had a medical degree with training in gastroenterology or have been a practicing physician, such as an internist, with experience in treating IBS.
8. The prior art includes the '608 patent (JTX 132), the Pimentel Book (PTX 752), Yang (DTX 892), the RFIB 2001 Press Release (DTX 657), Pimentel 2006 (JTX 53), the RFIB 2001 Protocol (DTX 340), Cuoco (JTX 38), Barrett (JTX 71), Viscomi 2005 (JTX 64), Lin 2006 (JTX 69), Lauritano (DTX 384), and Scarpellini (JTX 60).
9. The RFIB 2001 Protocol and Pimentel 2006 disclose all limitations of the IBS-D claims.
10. A POSA would have been motivated to combine the RFIB 2001 Protocol and Pimentel 2006 with a reasonable expectation of success.

11. As of the priority date, the prior art disclosed positive results in using rifaximin to treat IBS-D for a range of doses. The asserted IBS-D claims describe a dosing regimen within the known range.
12. A POSA would have had motivation to treat IBS-D patients 65 years of age or older with rifaximin. A POSA would have had a reasonable expectation of success in treating this patient group with rifaximin.
13. The prior art did not teach away from using rifaximin to treat IBS-D according to the claimed methods.
14. There was some skepticism in the literature.
15. The asserted IBS-D claims are invalid as obvious.
16. The specification describes "durability of response" as including adequate relief from symptoms for 12 weeks.
17. A POSA would recognize that the inventor possessed the claimed durability of response.
18. A POSA would have reasonable certainty regarding the meaning of "adequate relief" and "durability of response."

**2. Infringement**

**i. Age 65 and Over ('667 Patent, Claim 3)**

Claim 3 of the '667 patent requires administration of rifaximin to patients who are 65 years and older. I find that Norwich's label will induce administration to this patient population. Norwich's ANDA product is indicated for "adults." (JTX 73 § 1.3). "Adults" include people who are 65 years and older. The label's "Use in Special Populations" section describes "Geriatric Use." (JTX 73 § 8.5). The label states, "No overall differences in safety or effectiveness were observed between these subjects [aged 65 and over] and younger subjects for either indication." (*Id.*)

Accordingly, Norwich knows and specifically intends that its ANDA product will be used to treat IBS-D in patients who are 65 and older.

**ii. 12 Week Durability of Response ('569 Patent, Claim 2)**

Claim 2 of the '569 patent requires a "durability of response [that] comprises about 12 weeks of adequate relief." I find that Norwich's label will induce such a response in at least some patients. Salix argues, "By following [the dosing] instructions [on the label], some patients will inevitably have a durability of response comprising about 12 weeks of adequate relief." (D.I. 174 at 14). Salix's expert testified to this, and Norwich's expert admitted as much. (Tr. 537:12–540:4, 581:16–22 (agreeing that at least some patients "will experience adequate relief of their IBS-D symptoms for 12 weeks after taking rifaximin 550 milligrams three times a day for 14 days")). "[A]n accused product that sometimes, but not always, embodies a claimed method nonetheless infringes." *Bell Commc'ns Rsch., Inc. v. Vitalink Commc'ns Corp.*, 55 F.3d 615, 622–23 (Fed. Cir. 1995).

Norwich's label supports a finding of inducement. The product is indicated "for the treatment of irritable bowel syndrome with diarrhea." (JTX 73 § 1.3). The Clinical Studies section states, "The efficacy of rifaximin tablets for the treatment of IBS-D was established in 3 randomized, multi-center, double-blind, placebo-controlled trials in adult patients." (JTX 73 § 14.3). The third study, TARGET 3, tracked long-term response to treatment. In it, "382 [patients] experienced a period of symptom inactivity or decrease that did not require repeat treatment by the time they discontinued, including patients who completed the 22 weeks after initial treatment with rifaximin." (*Id.*). Norwich argues that TARGET 3 only measured two symptoms of IBS-D, rather than the claimed "adequate relief" of IBS-D symptoms, and that it reported "time to recurrence" rather than the claimed "durability of response." (D.I. 183 at 14).

Even when a proposed label does not exactly track the claim language, a package insert containing directives that will "inevitably lead some consumers to practice the claimed method" provides sufficient evidence for a finding of specific intent. *See AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1060 (Fed. Cir. 2010). Accordingly, I find that Norwich's label will induce some patients to experience a 12-week durability of response as required by the patents and that Norwich will have the specific intent to induce infringement.

**3. Obviousness**

Salix asserts that the definition of a POSA is not outcome determinative. (D.I. 181 at 16). Noriwch has proposed that a POSA would have had a medical degree with training in gastroenterology or have been a practicing physician, such as an internist, with experience in treating IBS. (D.I. 181 at 17). I adopt Norwich's definition of a POSA.

Norwich argues that, as of the priority date, rifaximin was known to be safe and effective in treating IBS-D. Prior to February 2008, there was widespread off-label use of Xifaxan to treat IBS in the United States. As of January 2008, 74% of gastroenterologists polled by Salix had prescribed Xifaxan for IBS. (DTX 349-130). Prescription data showed that 27.7% of Xifaxan 200 mg tablet uses in November 2007 had been for IBS. (DTX 349-89; Tr. 832:2-833:23).

The prior art also discussed using rifaximin to treat IBS. In 1999, Dr. Pimentel applied for patents on the use of rifaximin to treat IBS. (JTX 132; JTX 133; Tr. 617:1-21). The '608 patent claims a method of "treating a subject suffering from [IBS], comprising administering rifaximin to the subject . . ." (JTX 132 at cl. 1; Tr. 620:3-621:9).[2] At a 2005 conference hosted by Salix, Dr. Pimentel disclosed that his practice group had used rifaximin to treat about 900 patients. (Tr.

[2] The '608 patent issued in 2010 but the parties agree that it was publicly accessible before the priority date. (D.I. 149, Ex. 1 ¶ 136).

627:7-628:5; DTX 582-4, 5). In 2006, Dr. Pimentel published a book titled *A New IBS Solution, Bacteria – the Missing Link in Treating Irritable Bowel Syndrome*, which recommended the use of rifaximin as a safe and effective way to treat IBS-D. (PTX 752; Tr. 623:25-624:21).

In 2006, three studies were published on the use of rifaximin to treat IBS. A randomized, double-blind, placebo-controlled study found rifaximin to be more effective than placebo in improving IBS. ("Pimentel 2006," JTX 53). A retrospective chart review of IBS patients who had tested positive for small intestine bacterial overgrowth ("SIBO") reported a significant reduction in the number of patients having IBS symptoms 4-5 months after treatment, and that 12 of 23 patients had "complete resolution of IBS symptoms." ("Cuoco," JTX 38 at 94). Another retrospective chart review of 8 patients disclosed, "rifaximin use resulted in complete resolution of clinical symptoms in 4 patients, with no IBS relapse (follow-up, 1 to 6 months)," and "partial symptom improvement was observed in 4 patients, 3 of whom were treated for an additional 2 months with rifaximin 400 mg three times daily cycle therapy (2 weeks on / 1 week off []) which resulted in a 50% to 70% improvement from baseline." ("Barrett," JTX 71; Tr. 639:9-640:5).

Norwich proposes three prior art combinations involving three pieces of prior art. Because I agree that Pimentel 2006 in light of the RFIB 2001 Protocol renders the asserted claims of the IBS-D patents obvious, I will not address the other two combinations.

Pimentel 2006 administered rifaximin, 400 mg TID for 10 days, to treat IBS patients aged 18-65. Pimentel 2006 taught, "rifaximin resulted in statistically greater global improvement in IBS than placebo," and "[i]mprovements were sustained through 10 weeks of follow-up" after 10 days of treatment. (JTX 53 at 562).

The "RFIB 2001 Protocol" (DTX 340) was a Phase II trial designed to administer rifaximin to patients aged 18 and over, 550-2,220 mg per day for 14 days for the treatment of IBS-D. The

protocol included the outcome measures of providing adequate relief of symptoms and evaluating a durability of response over a 12-week post-treatment period. Salix announced the successful completion of this study on September 5, 2007 (the "RFIB 2001 Press Release") and disclosed, "Top-line results of this study demonstrate that . . . a 14-day course of rifaximin at 550 mg twice-a-day, provides a statistically significant improvement in both adequate relief of IBS symptoms and adequate relief of bloating, compared to placebo." (DTX 657-4; Tr. 656:12-657:10).

The RFIB 2001 Protocol and Pimentel 2006 disclose all limitations of the asserted IBS-D claims.

I find that a POSA would have been motivated to combine Pimentel 2006 with the RFIB 2001 Protocol and would have had a reasonable expectation of success. Pimentel 2006 reported sustained improvement in IBS symptoms for patients aged 18-65 for at least 10 weeks on a 400 mg TID, 10-day regimen. The RFIB 2001 Protocol included no upper age limit, a 14-day dosing regimen of 550 to 2200 mg per day, and the treatment of patients with IBS-D in particular. As of the priority date, a POSA would have known about the successful RFIB 2001 Protocol results. Widespread off-label use reflects a motivation to use rifaximin for the treatment of IBS-D with a reasonable expectation of success. As described above, several pieces of prior art reported success in treating IBS with rifaximin. The caselaw does not require "conclusive proof of efficacy." *Hoffmann-La Roche Inc. v. Apotex Inc.*, 748 F.3d 1326, 1331 (Fed. Cir. 2014). Rifaximin had been shown to be effective in treating IBS in Pimentel 2006 and IBS-D in the RFIB 2001 Protocol, which were randomized, placebo-controlled clinical trials. Together, I think this is strong evidence that a POSA would have a motivation to use rifaximin for the treatment of IBS-D.[3]

[3] The parties do not discuss whether there is any difference between the motivation to use rifaximin to treat IBS and to treat IBS-D. I think a POSA would have been motivated to treat IBS-D and would have had a reasonable expectation of success in doing so, even though much of

I also find that a POSA would have had the motivation to select an optimal dosing regimen from within the known range. The prior art describes positive results from a range of doses. Pimentel 2006 used 400 mg of rifaximin TID for 10 days and reported "global improvement in IBS." (JTX 53 at 558). Cuoco disclosed a total dose of 1200 mg for 14 days and reported significant reduction in the number of patients having IBS symptoms. (JTX 38 at 91). Barrett disclosed 400 mg TID for 1-5 months. (JTX 71). In 2007, Quigley explained, "Antibiotic dose and duration of therapy have not been established. All studies to date have used different doses and antibiotic regimens; the optimal approach needs to be established in a prospective, placebo-controlled, dose-ranging study." (PTX 692 at 1142). The RFIB 2001 Protocol taught a range from 1100 mg to 2200 mg per day for 10-14 days. (Tr. 655:20-656:11). The RFIB 2001 Press Release reported that a "14-day course of rifaximin at 550 mg twice-a-day" dosage saw effective results. (DTX 657-4). The claimed dose is 550 mg of rifaximin TID for 14 days.

"Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or working ranges by routine experimentation." *In re Applied Materials, Inc.*, 692 F.3d 1289, 1295 (Fed. Cir. 2012) (cleaned up). Here, a POSA would have been motivated to combine the prior art to achieve a dosage regimen within the known range. Salix's market research showed that 56% of physicians who prescribed Xifaxan for IBS used TID dosing and 62% had prescribed the drug to be taken for 10-14 days. (DTX 349-131). This market research is not prior art because it was not publicly available as of the priority date, but it reflects a POSA's state of mind. Pimentel 2006 taught, "Recent data suggest that the optimal dosage of rifaximin may, in fact, be higher than that used in our study." (JTX 53 at 562). A POSA would have been

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the prior art describes the treatment of "IBS." About one third of IBS patients have IBS-D, and there is no evidence in the record that a POSA would expect an IBS-D patient to respond differently to treatment than a patient with another form of IBS. (Tr. 622:21-623:1).

motivated to use TID dosing to maintain an effective concentration of rifaximin in the small intestine to control bacteria levels. (Tr. 672:4-23). Finally, a POSA would have been motivated to improve the use of rifaximin to treat IBS by using a larger tablet to reduce patients' pill burden and improve compliance. (Tr. 674:1-16.).[4]

I further find that a POSA would have had the motivation to treat patients 65 years of age or older with a reasonable expectation of success. The prior art described rifaximin use to treat symptoms of IBS-D patients 65 years or older. (JTX 71 at 1-2; DTX 340-7; DTX 657-4). A POSA would have expected the effect observed in Pimentel 2006 to apply to older patients too. (Tr. 679:12-16).

Salix attacks Norwich's obviousness case on several fronts.

Salix argues that a POSA would recognize these prior art sources as flawed. Cuoco, for instance, is based on the unproven premise that SIBO contributed to IBS-D. Furthermore, its methodology was poor. (D.I. 181 at 19). Barrett was a retrospective chart review of only 8 patients and concluded that more research was needed. (*Id.*). Pimentel 2006 did not find an improvement in the symptoms of abdominal pain and diarrhea. (JTX 53 at 561). An editorial by Dr. Drossman noted that Pimentel 2006's limitations made its "findings inconclusive and raise[d] questions about the clinical significance of the results." (PTX 457 at 627; Tr. 767:11-18, 770:10-19). Finally, Salix argues that the RFIB 2001 Protocol did not disclose results, and "it was unrebutted that a

[4] Salix argues that Dr. Harary undermined his own testimony on the pill burden. Dr. Harary testified, "I don't think going from two pills to one pill would make a big difference, but if you have a larger number of pills, then going to one pill would be – would be convenient and the patients would be more comfortable taking them." (Tr. 674:12–16). As of the priority date, only 200 mg pills were available. I take Dr. Harary's testimony to be saying that three 200 mg pills would be needed to achieve a similar dose (600 mg, as opposed to the claimed 550 mg), and that three pills are more inconvenient than one pill. Accordingly, I do not see how Dr. Harary undermined his own testimony regarding pill burden.

POSA would not have reasonably expected RFIB2001 would be successful simply because the trial had begun." (D.I. 181 at 19–20).

I am unpersuaded by these arguments. It is fair to critique sources, and a POSA would take a source's shortcomings into consideration when evaluating the evidence. Obviousness does not require perfect evidence, however, and the available evidence persuaded a significant number of doctors who would have been qualified as POSAs to use rifaximin to treat IBS. Regarding Pimentel 2006's failure to find an improvement in abdominal pain and diarrhea, the patents are not directed to specific symptoms but to "adequate relief." There are many symptoms of IBS-D. The patents themselves do not claim relief from every symptom.

Finally, I find that Salix's press release disclosing success in the RFIB 2001 Protocol study is prior art, and thus a POSA would have known about the RFIB 2001 top-line results as of the priority date. Salix argues that the press release was derived from the inventor's work and thus cannot be prior art. (D.I. 181 at 20 (citing *Invitrogen Corp. v. Biocrest Mfg., L.P.*, 424 F.3d 1374, 1380-81 (Fed. Cir. 2005))). Norwich argues that Salix has waived this contention by failing to raise it in the Pretrial Order. (D.I. 185 at 8). Upon review of the Pretrial Order and its Exhibits (D.I. 147-149), I see Plaintiffs' acknowledgement that Norwich is asserting the press release as prior art (D.I. 149, Ex. 4, at 5 n.2), and I see a list of items the prior art status of which Plaintiffs contest, which does not include the press release (*id.* at 6 ¶28), and I do not see any discussion of derivation, so the argument is likely waived. But I do not need to decide waiver, however, because there is no evidence upon which to make a factual finding that the press release was derived from the inventor's work. "Since appellees have produced no evidence—unsurprising given their belated recourse to this argument—and provided no supported explanation demonstrating that the Brandt references were in fact printed publications authored by Dr. VanDenburgh for the purposes

of § 102(a), we see no reason to remand to make further findings on this issue." *Allergan, Inc. v. Apotex Inc.*, 754 F.3d 952, 969 (Fed. Cir. 2014). The *Allergan* Court thus concluded that the printed publications at issue were prior art. *Id.* at 969–70). The press release is therefore prior art. Its disclosure of positive results would give a POSA a reasonable expectation of success in using rifaximin to treat IBS-D.

Salix also points to skepticism in the literature regarding the connection between SIBO and IBS and whether to use antibiotics to treat IBS-D. Drossman criticized the Pimentel 2006 methodology, as discussed above. A 2007 Education Practice note by Eamonn M.M. Quigley stated, "sound rationale for antibiotic therapy ha[d] not been established because the issue of SIBO in IBS ha[d] not been resolved." (PTX 692 at 1142; Tr. 777:20–21). Indeed, Salix argues, using antibiotics would have drawbacks: antibiotics could "exacerbate symptoms" or "lead to antibiotic resistance and opportunistic infections" like *c. difficile*. (PTX 664 at 1780; PTX 692 at 1142). A February 4, 2008 article by Vanner considered the evidence and concluded that there was insufficient evidence to recommend the use of antibiotics to treat IBS. (Tr. 779:3–8). Accordingly, Salix argues that the off-label use is best understood as physicians acting out of "desperation, not because they expected it to work." (D.I. 181 at 17).

Upon review of the evidence, it appears that IBS is a complex disease and the pathogenesis was unknown as of the priority date. The relationship between IBS and SIBO was actively being explored, provoking a debate within the field. Quigley, Vanner, and Drossman do not teach away from using rifaximin to treat IBS, and Salix does not argue that they do. Based on the evidence, I do not think a POSA would elevate these sources above the other prior art available. The RFIB 2001 Press Release—which was not cited by Quigley, Vanner, or Drossman—states, "The belief that bacteria in the small bowel may play a role in the symptoms of IBS gains additional evidence

with this large, multicenter trial." (DTX 657-4). I do not think a POSA would have discounted prior art sources that were based upon the theory that SIBO contributed to IBS because studies such as the RFIB 2001 Protocol were testing that hypothesis at the time. More importantly, a POSA would look to the top-line results from the RFIB 2001 Protocol as evidence that rifaximin could be effective in treating IBS-D, regardless of whether the results were based upon a link between IBS-D and SIBO.

Regarding the concerns of bacterial resistance, expert testimony shows that short-term administration did not raise resistance concerns. (Tr. 493:15-494:20). Furthermore, in 2007, a retrospective study of 84 IBS patients who were retreated with rifaximin noted that 69% of patients had a "clinical response" to rifaximin and that retreatment did not result in clinically relevant antibiotic resistance. (DTX 892-2, 5; Tr. 630:5-19, 631:9-18).

Accordingly, I do not think these concerns would dissuade a POSA from exploring the use of rifaximin in treating IBS-D. The 74% of gastroenterologists who had reported using rifaximin for IBS-D patients is real world evidence supporting the conclusion that there was a motivation to explore this treatment, despite the potential risks.

Regarding secondary considerations, Salix argues that there was skepticism that the claimed dosing regimen could safely and effectively treat IBS-D. (D.I. 174 at 17). Salix points to statements in Quigley, Drossman, and Vanner such as, "A sound rationale for antibiotic therapy has not been established . . . . ," and, "There is insufficient evidence to recommend antibiotics for the treatment of [IBS] at present." (PTX 692 at 1142; PTX 693 at 1319). Furthermore, experts on the FDA advisory committee stated that using rifaximin 550 TID for 14 days was "a completely different paradigm and a different treatment structure," and that Salix had proposed to "treat[] a disease which we know nothing or very little about with a drug that we know little or nothing

about." (PTX 535 at 302, 307). The FDA advisory committee also expressed concern about antibiotic resistance. (*Id.* at 137).

Norwich responds that Salix's evidence of skepticism "fails" because rifaximin had already been used to safely and effectively treat IBS-D before 2008. (D.I. 183 at 18). I do not think this negates Salix's evidence of skepticism.

Regarding skepticism in the literature, Norwich argues that one of the articles was published before Yang and the RFIB 2001 Press Release, and the other two articles did not cite those references. (*Id.* at 20). I agree that evidence of skepticism is not as powerful when the skepticism is expressed by a source unfamiliar with the "prior art references that laid the groundwork for the inventors' experiments." *PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342, 1365 (Fed. Cir. 2007). I still give some weight to these articles, especially Vanner, which was published less than a month before the priority date.

Regarding the FDA advisory committee, Norwich argues, "The cited passages from the 2011 FDA advisory committee meeting regarding the IBS-D indication did not criticize the safety or effectiveness of rifaximin to treat IBS-D in at least some patients." (*Id.* at 19). Norwich's expert did not address the FDA statements. I decline to adopt attorney argument in place of expert testimony.

Ultimately, I give some weight to Salix's evidence of skepticism from the literature and the FDA's statements. I do not think these experts "expressed disbelief," *United States v. Adams*, 383 U.S. 39, 52 (1966), but there is a "range of third-party opinion that can constitute skepticism." *Neptune Generics, LLC v. Eli Lilly & Co.*, 921 F.3d 1372, 1378 (Fed. Cir. 2019). Ultimately, Salix has shown a small amount of skepticism but not enough to change the outcome of the obviousness analysis.

I find that the asserted IBS-D claims are invalid as obvious.

**4. Written Description**

Norwich argues that asserted claim 2 of the '569 patent lacks written description because it fails to show possession of the claimed "durability of response compris[ing] about 12 weeks of adequate relief of symptoms." (D.I. 176 at 30). The specification explains:

> As used herein, 'durability of response' includes for example, adequate relief of symptoms after removal of treatment, continuous adequate relief of symptoms after removal of treatment, or response that is greater than or superior to placebo response. . . . The duration of response, may be, for example, 2 days, 7 days, two weeks, 3 weeks, 4 weeks, 12 weeks, between about 1 week and about 24 weeks or longer.

'569 Patent at 11:44–53. The specification also discloses a proposed study design in Figure 3 "to show durability of response." *Id.* at 6:10–12. Figure 3 shows a "4 Week Treatment Period" follow by a 12 week "Post-Treatment Phase." *Id.* at Fig. 3, 25:55–59. I think this is enough to show possession of the claimed 12-week durability of response.

Norwich argues that the disclosure is "effectively unlimited in time." (D.I. 176 at 31). "[T]he level of detail required to satisfy the written description requirement varies depending on the nature and scope of the claims and on the complexity and predictability of the relevant technology." *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010). Here, the evidence shows that IBS-D is a complex disease and that not all patients achieve a 12-week durability of response. A POSA would recognize that the inventor adequately described a range of possibilities for the durability of response and was in possession of the claimed 12-week period.

**5. Indefiniteness**

Norwich argues that asserted claim 2 of the '569 patent is invalid as indefinite. (D.I. 176 at 28). As noted, Claim 2 includes the limitation, "durability of response compris[ing] about 12 weeks of adequate relief of symptoms." Norwich argues that "adequate relief of symptoms" is

subjective opinion. (*Id.*). Salix responds that "adequate relief" and "durability of response" have accepted meanings to a POSA. (D.I. 181 at 31). IBS-D is a collection of symptoms and there is no biomarker to determine a successful overall treatment of IBS-D. (Tr. 507:24-508:7). I credit Dr. Schoenfeld's testimony that patient-reported "adequate relief" is used to determine IBS-D treatment success in the field. (Tr. 519:15-22; 821:9-822:1). Thus, I reject Norwich's argument that claim 2 of the '569 patent is invalid as indefinite.

## V. CONCLUSION

For the foregoing reasons, Norwich's ANDA will induce infringement of the HE, IBS-D, and Polymorph patent claims. The HE claims are nonobvious and Norwich has failed to show a lack of adequate written description. The asserted Polymorph and IBS-D claims are invalid as obvious.

I will enter a final judgment in accord with the conclusions of this opinion.

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

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| SALIX PHARMACEUTICALS, LTD.; SALIX PHARMACEUTICALS, INC.; BAUSCH HEALTH IRELAND LTD.; ALFASIGMA S.P.A.,<br><br>Plaintiffs,<br><br>v.<br><br>NORWICH PHARMACEUTICALS, INC.,<br><br>Defendant. | Civil Action No. 20-430-RGA |

MEMORANDUM

The parties have a dispute concerning the final judgment. (D.I. 190). I am entering a final judgment in accordance with the following rationale.

Plaintiffs sued Defendant under § 271(e)(2)(A) of the Patent Act for submitting an abbreviated new drug application ("ANDA") to the Food and Drug Administration ("FDA"). At trial, Plaintiffs asserted three patent families against Defendants: one on the product, one on the hepatic encephalopathy indication (the "HE indication"), and one on the irritable bowel syndrome with diarrhea indication (the "IBS-D indication"). After a bench trial, I determined that only the patents on the HE indication were both not invalid and infringed by Norwich's proposed ANDA.

The parties dispute whether the final judgment ought to order the FDA approval date for "Norwich's ANDA No. 214369" or "Norwich's ANDA with proposed labeling containing [the HE indication]" as the expiry date of the HE patents. (D.I. 190).

35 U.S.C. § 271(e)(2)(A) makes it an "act of infringement to submit" an ANDA "for a drug claimed in a patent or the use of which is claimed in a patent." Because the ANDA's HE indication would infringe Plaintiffs' patents, the ANDA submission is an act of infringement. In such cases, the Patent Act states, "the court shall order the effective date of any approval of the drug . . . involved in the infringement to be a date which is not earlier than the date of the expiration of the patent which has been infringed." 35 U.S.C. § 271(e)(4). Thus, the effective date of the approval of this infringing ANDA must not be earlier than the expiration of the latest asserted HE claim.

The scope of my ruling is that the HE patents are not invalid, and that the HE indication would infringe the HE patents. Norwich's proposed ANDA has the HE indication. I cannot rule on facts that are not before me. That Norwich may seek to carve out the HE indication as permitted by 21 U.S.C. § 355(j)(2)(A)(viii) is immaterial to this analysis. That label is not before me.

The parties dispute whether I ought to enter injunctive relief. (D.I. 190 at 2, 4). I have never had a hearing on whether injunctive relief should issue after a finding of ANDA infringement, or so far as I can recall, even an argument in a pleading that it should not issue.[1] An injunction seems unlikely to make a practical difference when only method patents are not invalid and infringed. The only reason I would enter an injunction directed at Defendant would be to enjoin infringing activity that could be undertaken in the absence of FDA approval. But, the absence of FDA approval blocks direct infringement of the HE method claims. Without that direct infringement, Defendant cannot induce infringement. An injunction would therefore be redundant of the order barring FDA approval, because the FDA cannot approve the ANDA

[1] There have been disputes about the details of the injunctive language.

before the patents expire. For that reason, I suspect it will be difficult for Salix to show irreparable harm. *See Alcon, Inc. v. Teva Pharms. USA, Inc.*, 2010 WL 3081327, at *2 (D. Del. Aug. 5, 2010). Should Salix have a good faith belief that it is entitled to an injunction, it can file a motion to reconsider the matter, and I will reconsider the matter.

So entered this 10th day of August 2022.

United States District Judge

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

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| SALIX PHARMACEUTICALS, LTD.; SALIX PHARMACEUTICALS, INC.; BAUSCH HEALTH IRELAND LTD.; ALFASIGMA S.P.A., | ) | |
| Plaintiffs, | ) | C.A. No. 20-430 (RGA) |
| v. | ) | |
| NORWICH PHARMACEUTICALS, INC., | ) | |
| Defendant. | ) | |

**FINAL JUDGMENT**

This action, having been tried before the Court from March 21 through March 25, 2022, and the Court having issued an opinion after trial (D.I. 191):

IT IS HEREBY ORDERED and ADJUDGED:

1. Judgment is entered in favor of Plaintiffs Salix Pharmaceuticals, Ltd., Salix Pharmaceuticals, Inc., Bausch Health Ireland Ltd., and Alfasigma S.p.A. (collectively, "Plaintiffs") and against Defendant Norwich Pharmaceuticals, Inc. ("Norwich") on Plaintiffs' claim that Norwich will induce infringement of claim 8 of U.S. Patent No. 8,642,573 (the "'573 Patent"), claim 6 of U.S. Patent No. 9,421,195 (the "'195 Patent"), and claims 11-12 of U.S. Patent No. 10,335,397 (the "'397 Patent").in connection with Norwich's proposed generic rifaximin 550 mg tablets ("ANDA Product") that are the subject of Norwich's Abbreviated New Drug Application ("ANDA") No. 214369.

2. Judgment is entered in favor of Plaintiffs and against Norwich on Norwich's counterclaims for non-infringement and invalidity of claim 8 of the '573 Patent, claim 6 of the '195 Patent, and claims 11-12 the '397 Patent.

3. Judgment is entered in favor of Plaintiffs and against Norwich that pursuant to 35 U.S.C. § 271(e)(2), Norwich's submission of Norwich's ANDA No. 214369 was an act of infringement of claim 8 of the '573 Patent, claim 6 of the '195 Patent, and claims 11-12 the '397 Patent.

4. Judgment is entered in favor of Norwich and against Plaintiffs on Norwich's counterclaims for invalidity of claim 2 of U.S. Patent No. 8,309,569, claim 3 of U.S. Patent No. 10,765,667, claim 4 of U.S. Patent No. 7,612,199, and claim 36 of U.S. Patent No. 7,902,206.

5. Pursuant to 35 U.S.C. § 27l(e)(4)(A), it is hereby ordered that the effective date of any final approval by the Food and Drug Administration ("FDA") of Norwich's ANDA No. 214369 is to be a date not earlier than the date of expiration of the last to expire of the '573, '195, and '397 Patents (currently October 2, 2029), plus any regulatory exclusivity to which Plaintiffs are or become entitled. Norwich shall notify the FDA of this judgment within two (2) business days of its entry (with a copy of such notice given simultaneously to Plaintiffs).

6. In the event that a party appeals this Final Judgment, any motion for attorneys' fees and/or costs under Fed. R. Civ. P. 54 and/or Local Rules 54.1 or 54.3, or any motion that this case is exceptional under 35 U.S.C. § 285, shall be considered timely if filed and served within thirty (30) days after final disposition of any such appeal.

SO ORDERED this 10th day of August, 2022.

United States District Judge

**IN THE UNITED STATES DISTRICT COURT**

**FOR THE DISTRICT OF DELAWARE**

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| SALIX PHARMACEUTICALS, LTD.; SALIX PHARMACEUTICALS, INC.; BAUSCH HEALTH IRELAND LTD.; ALFASIGMA S.P.A.,,<br><br>Plaintiffs,<br><br>v.<br><br>NORWICH PHARMACEUTICALS, INC.,<br><br>Defendant. | Civil Action No. 20-430-RGA |

**MEMORANDUM ORDER**

I filed a final judgment in this case. (D.I. 193). Shortly thereafter, Defendant filed a motion to modify that judgment pursuant to Federal Rule of Civil Procedure 60(b). (D.I. 205). Subsequent briefing made clear that Defendant was primarily relying upon Rule 60(b)(5), which provides: "On motion and just terms, the court may relieve a party . . . from a final judgment, order, or proceeding for the following reasons: . . . (5) the judgment has been satisfied, released, or discharged; it is based on an earlier judgment that has been reversed or vacated; or applying it prospectively is no longer equitable." Plaintiffs oppose the motion. (D.I. 213).

The background to the pending motion is that Defendant filed an ANDA seeking to make and market a drug for two different methods of treatment—the IBS-D indication and the HE indication. I had a bench trial. After trial, I ruled in Defendant's favor on the IBS-D indication (as well as the composition claims), finding all patent claims asserted in relation to those two issues

to be invalid. I ruled in Plaintiffs' favor only on the HE indication, finding all claims asserted in relation to that issue to be infringed and not invalid. In the final judgment, I ordered the FDA not to approve the ANDA before the latest expiration (in about 2029) of the patents on which Plaintiffs won. About a month after entry of the final judgment, Defendant filed an amended ANDA that purports to carve out everything relating to the HE indication. Defendant says, if the FDA approves the amended ANDA, Defendant would not be inducing infringement by marketing the pharmaceutical with the amended label. Other than providing the proposed label, Defendant has refused to provide any other information about the amended ANDA, including its status with the FDA or anything else.

I do not think Defendant's request fits in comfortably with the requirements of Rule 60(b)(5), and I do not think, even if it did, that it could be resolved in the summary fashion that Defendant seems to think it should be.

First, the Rule. Defendant says the judgment has been "satisfied," but I think it is pretty clear that the "satisfied, released, or discharged" language is talking about money, and is therefore inapplicable. Defendant says the injunction prohibiting FDA approval before 2029 is "no longer equitable" because Defendant no longer seeks to do the act that was the basis for the injunction. The case law says that Rule 60(b)(5) is for a significant change in circumstances. *See Rufo v. Inmates of Suffolk Cnty. Jail*, 502 U.S. 367, 383 (1992). While such a change in circumstances does not have to be entirely unforeseeable, a "modification should not be granted where a party relies upon events that actually were anticipated at the time" the final judgment was entered. *Id.* at 385. I do not think "changed circumstances" applies here. The case was tried as essentially three independent up-or-down decisions. In my experience with ANDAs, it is common, and certainly not rare, to have split decisions. ANDA practitioners and pharmaceutical companies

surely know this. Thus, there were a limited number of possible outcomes at trial. But, of course, the trial results are not the changed circumstances, as the actual outcomes were previewed two weeks before the final judgment (D.I. 189) and disclosed at the same time as the final judgment. The only changed circumstance is that Defendant decided to amend its ANDA, which it filed on September 6, 2022 (D.I. 206 at 2), nearly one month after the final judgment. The changed circumstance is simply a voluntary decision of the trial loser to change course, which is neither unanticipated nor unforeseeable.

I also wonder about "equitableness" generally. Defendant made various strategic choices along the way, but now does not want to live with the consequences of those choices.[1] Defendant says that it is now worse off than other generics that settled with Plaintiffs and apparently can launch in 2028. While true, Defendant does not argue that it could not have settled and gotten the same deal as the other generics. Defendant says that it has gone to the effort of proving the asserted composition and IBS-D patent claims invalid, so other generics will be able to enter the market a lot sooner than 2028 by taking advantage of Defendant's accomplishments.[2] Defendant suggests this is inequitable (and perhaps it is), but the inequity does not exist between Plaintiffs and Defendant. To the extent there is inequity, it is between Defendant and other generics. Defendant says that the public will be harmed because Plaintiffs will not have any generic competition (with attendant lower costs) on the IBS-D treatment method for some period of time, even though

[1] I was assigned one related ANDA, where Defendant was only seeking approval to market the IBS-D indication, and not the HE indication. *Salix Pharms., Ltd. v. Sun Pharms. Inds., LTD*, No. 19-734-RGA (D.Del. filed April 24, 2019). That Defendant quickly resolved its case with Plaintiffs.

[2] This may be a bit speculative too, because Plaintiffs have lots of relevant patents and patent claims, and, while presumably they advanced their best claims at the trial in this case, I would expect they have more listed in the Orange Book to assert against the next generic to file an ANDA.

Plaintiffs have no right to a monopoly on that treatment method. This is a bit speculative, since there is no information about if or when the FDA might approve the amended ANDA.

Second, the record. It is not a simple matter to determine whether an ANDA applicant has successfully carved out language from a label to turn infringement into non-infringement.[3] Defendant, other than saying it has successfully carved out the HE indication, and providing me the label, has presented no evidence in support of its assertion. Further, Rule 60(b) "does not allow relitigation of issues that have been resolved by the judgment." 11 WRIGHT, MILLER, & KANE, FEDERAL PRACTICE AND PROCEDURE § 2863, at 459 (3d ed. 2012). Defendant presents no facts indicating that it could not have litigated the carve-out or that it was denied a full and fair opportunity to do so. *Allergan, Inc. v. Sandoz Inc.*, 2013 WL 6253669, at *3 (E.D. Tex. Dec. 3, 2013), *aff'd*, 587 F. App'x 657 (Fed. Cir. 2014). As in *Allergan*, Defendant fully litigated the merits of its non-infringement and invalidity case, lost, and now seeks a way around the final judgment through Rule 60(b) that "is tantamount to seeking summary judgment premised on new allegations that only came to exist after the final judgment was rendered . . . ." *Id.*

Defendant states that Plaintiffs have not tried to state a claim against the carve out, and therefore, they cannot. I am unpersuaded that Plaintiffs have some duty now to state a claim on something that Defendant never raised as an issue before entry of final judgment. It is not surprising that Defendant has cited no case that requires a plaintiff to be able to state a claim on a new issue after judgment. What Defendant wants would essentially be a second litigation.

[3] I had an ANDA trial in January 2023 where one of the issues is whether the carve out has been successful. The issue is hotly disputed. *See Sanofi-Aventis U.S. LLC v. Sandoz, Inc.*, No. 20-804-RGA, D.I. 355 at 2 (D.Del. Feb. 17, 2023) (arguing non-infringement because Sandoz removed certain information from its proposed label).

Third, the law. Plaintiffs say, and Defendant does not present any argument to the contrary, that what Defendant seeks is unprecedented in an ANDA case. I am hesitant to be the first, because it just seems wrong to me that Defendant can litigate a case through trial and final judgment based on a particular ANDA, and then, after final judgment, change the ANDA to what it wishes it had started with, and win in a summary proceeding.

Thus, I DENY Defendant's Rule 60(b) motion. (D.I. 205).

IT IS SO ORDERED this 17th day of May, 2023.

United States District Judge

## CERTIFICATE OF COMPLIANCE WITH RULE 32(A)

1. This brief complies with the type-volume limitations of Federal Rule of Appellate Procedure 32(a)(7)(B) because this brief contains 13,276 words, excluding the parts of the brief exempted by Federal Rule of Appellate Procedure 32(f).

2. This brief complies with the typeface requirements of Federal Rule of Appellate Procedure 32(a)(5) and the type-style requirements of Federal Rule of Appellate Procedure 32(a)(6) because this brief has been prepared in a proportionally spaced typeface using Microsoft Office 365 in Times New Roman 14-point font.

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